

PCT

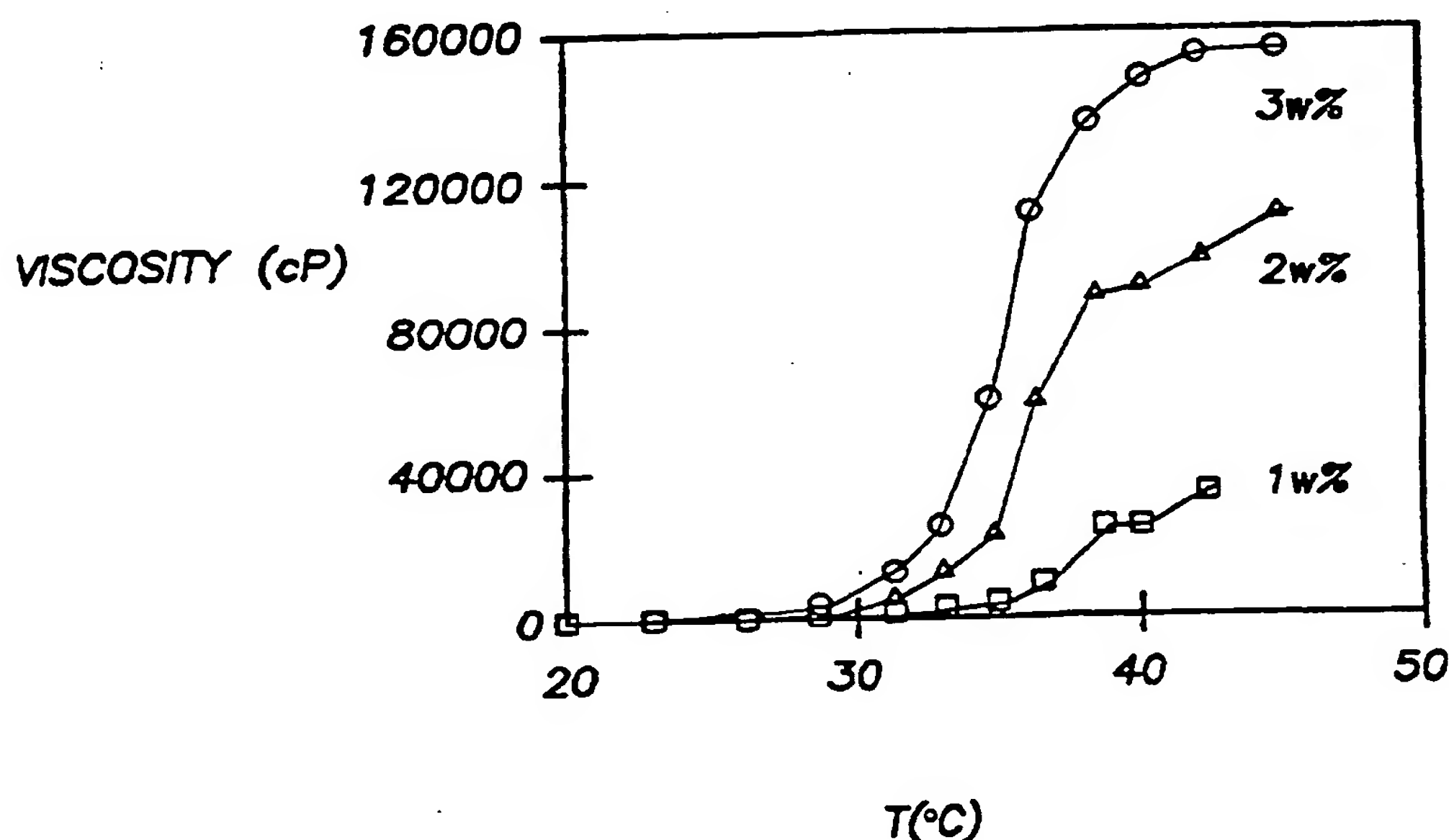
WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C08G		A2	(11) International Publication Number: WO 97/00275
			(43) International Publication Date: 3 January 1997 (03.01.97)
(21) International Application Number: PCT/US96/10376		(01720 (US). MCKINNEY, George, W., III [-/US]; 33 Old Orchard Road, Chestnut Hill, MA 02167 (US). ORKISZ, Michal [-/US]; 12 Hatherly Road, Brighton, MA 02135 (US). HAND, Barry [-/US]; 7 Arlington Drive, Monroe, NY 01950 (US).	
(22) International Filing Date: 14 June 1996 (14.06.96)			
(30) Priority Data:			
60/000,208 16 June 1995 (16.06.95) US 60/000,312 19 June 1995 (19.06.95) US 60/008,053 30 October 1995 (30.10.95) US 08/580,986 3 January 1996 (03.01.96) US 60/011,506 12 February 1996 (12.02.96) US 60/012,221 21 February 1996 (21.02.96) US 60/012,869 3 March 1996 (03.03.96) US 60/012,868 5 March 1996 (05.03.96) US 60/017,158 20 May 1996 (20.05.96) US			
(71) Applicant (for all designated States except US): GEL SCIENCES, INC. [US/US]; 213 Burlington Road, Bedford, MA 01730 (US).		(74) Agent: SCOZZAFAVA, Mary, Rose; Choate, Hall & Stewart, Exchange Place, 53 State Street, Boston, MA 02109 (US).	
(72) Inventors; and (75) Inventors/Applicants (for US only): BROMBERG, Lev [-/US]; 24 Mace Place #3, Lynn, MA 01902 (US). LUPTON, E., Cornelius [-/US]; 23 Pinckney Street, Boston, MA 02114 (US). SCHILLER, Matthew, E. [-/US]; 23C Sagamore Way, Waltham, MA 02154 (US). TIMM, Mary, J. [-/US]; Unit A1, 209 Great Road, Acton, MA		(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).	
		Published Without international search report and to be republished upon receipt of that report.	

(54) Title: RESPONSIVE POLYMER NETWORKS AND METHODS OF THEIR USE



(57) Abstract

A polymer network exhibiting the property of reversible gelation in response to a change in an environmental stimulus is provided. The solvated network polymer, comprises about 0.01 to 20 wt.% of an associating component linked to about 0.01 to 20 wt.% of a solvophilic component. The solvated composition exhibits at least a five-fold increase in viscosity upon gelation. The gelation may be triggered by a change in an environmental stimulus, such as temperature, pH and ionic strength.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Larvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
EE	Estonia	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	UG	Uganda
FI	Finland	MN	Mongolia	US	United States of America
FR	France	MR	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

Responsive Polymer Networks and Methods of Their Use

Field of the Invention

5 The present invention relates to a polymer composition which exhibits a reversible gelation in response to a change in temperature or other environmental stimulus. More particularly, the present invention is directed to a viscosifying polymer network that can be designed to reversibly gel over a wide range of conditions to provide a composition having a controllable range of viscosities, making it useful in a variety of pharmaceutical, cosmetic and industrial applications.

10

Background of the Invention

A polymer network is a special type of polymer-polymer composition having favorable interactions between the constituent polymers on a molecular level. Many polymer networks of the prior art utilize covalent bonding between the constituent
15 polymers to establish a permanent network structure. In addition to covalent bonding, interactions which promote the formation of a polymer network include coulombic attraction in the case of polyelectrolyte network complexes, hydrogen bonding in the case of polyether:poly(carboxyvinyl) complexes or Van der Waals attractions in case of nonpolar polymers. In addition to these types of interactions, physical interactions,
20 such as entanglement, contribute to the interacting nature of these systems. Because of the nature of these interactions, interpolymer systems may possess unique synergistic properties that none of the constituent polymers alone exhibit.

The capability of one component of a network to influence one or more components of a network during synthesis is known. As an example, a preformed
25 polymer may be used as a template in the polymerization of a second polymer. It has been established that the rate of polymerization and the polymerization molecular weight of poly(acrylic acid) is affected by the template polymer used for template polymerization. Adachi *et al.* (*Polymer J.* 14(12):985-992 (1982)) report that polymerization of acrylic acid in the presence of polyoxyethylene resulted in an
30 interpolymer complex having a ladder-like structure in which each oxyethylene residue forms a hydrogen bond with an acrylic acid residue.

The ability to form polymer:polymer complexes provides a stable composition of two or more polymers. Thus, it is desirable to provide polymer network compositions which possess all the properties of constituent polymers, but which have
35 improved stability and compatibility over simple blends of the constituent polymers. It is also desirable to provide polymer network compositions in which a synergistic effect

between the constituent polymers impart properties not possessed by the constituent polymers, either alone or in a simple blend.

Tanaka *et al.* (U.S. Patent No. 5,503,893) discloses a polymer network in which the interpolymer attractions are strong enough to permit a three-dimensional polymer network without the use of covalent crosslinking between the constituent polymers. The polymer composition of Tanaka is a gel which exhibits a volume change in response to an external trigger.

Reversibly gelling solutions are known. Efforts have been directed to the development of gelatinous drug delivery systems for topical applications and for ophthalmic delivery to the eye. Such reversibly gelling systems are useful wherever it is desirable to handle a material in a fluid state, but performance is preferably in a gelled or more viscous state.

A known material with these properties is a thermosetting gel using poloxamers, available commercially as Pluronic®, which is described in U.S. Patent No. 4,188,373. Adjusting the concentration of the polymer gives the desired liquid-gel transition. However, concentrations of the poloxamer of at least 15-20 % by weight are needed to produce a composition which exhibits such a transition at commercially or physiologically useful temperatures. Also, solutions containing 15-20 % by weight of responsive polymer are typically very viscous even under the lower viscosity state of responsiveness, so that these solutions can not function under conditions where low viscosity, free-flowing characteristics are required prior to transition. In addition, these polymer concentrations are so high that the material itself may cause unfavorable interactions during use.

Another known system which is liquid at room temperature, but forms a semi-solid when warmed to about body temperature is formed from tetrafunctional block polymers of polyoxyethylene and polyoxypropylene condensed with ethylenediamine, commercially available as Tetronic® poloxamers. These compositions are formed from approximately 10% to 50% by weight of the polyoxamer in an aqueous medium. See, U.S. Patent No. 5,252,318.

Joshi *et al.* in U.S. Patent No. 5,252,318 reports reversible gelling compositions which are made up of physical blend of a pH-sensitive gelling polymer (such as a cross-linked polyacrylic acid) and a temperature-sensitive gelling polymer (such as methyl cellulose or block copolymers of polyoxyethylene and polyoxypropylene). In compositions including methylcellulose, 5- to 8-fold increases in viscosity are observed

upon a simultaneous change in temperature and pH for very low methylcellulose levels (1-4% by weight). See, Figs. 1 and 2 of Joshi *et al.* In compositions including Pluronic® and Tetronic® poloxamers, commercially available forms of polyoxyethylene/polyoxypropylene block copolymer, commercially useful increases in viscosity (5- to 8-fold) upon a simultaneous change in temperature and pH are observed only at much higher polymer levels (> 12% by weight). See, Figs. 3-6 of Joshi *et al.*

WO 95/24430 published September 14, 1995, describes graft and block copolymers of component temperature-sensitive polymers and a pH-sensitive polymers. The graft and/or block copolymers possess a lower critical solution temperature (LCST) or cloud point between 20 °C and 40 °C at a pH of 6.0-8.0. The LCST represents the temperature at which the polymer phase separates from the solvent. This results in an opaque or translucent mixture or suspension. In medical applications, particularly ophthalmic applications, this undesirable.

Thus, the known systems which exhibit reversible gelation are limited in that they require large solids content and/or in that the increase in viscosity are less than 10-fold and/or exhibit a cloud point before viscosification.

Summary of the Invention

It is an object of the present invention to provide polymer network compositions which are capable of reversible gelation or viscosification, which have improved visual clarity and which have improved stability over simple blends of the constituent polymers.

It is a further object of the invention to provide polymer network compositions which exhibit gelation or viscosification at very low solids content.

It is another object of the present invention to provide polymer network compositions which exhibit a synergistic effect between the constituent polymers to impart properties not possessed by the constituent polymers, either individually or in a simple blend.

It is yet a further object of the invention to provide a method of making a polymer network compositions in an simple, economic and efficient means of production.

It is a further object of the present invention to provide a responsive polymer network composition having improved flow and gelation characteristics as compared to properties possessed by conventional reversible gelation compositions.

It is yet a further object of the invention to provide a polymer network composition which is transparent or translucent to light both before and after gelation.

It is yet a further object of the invention to provide new and useful devices, articles and compositions incorporating the viscosifying polymer network composition of the present invention, which take advantage of the reversible gelation properties of the polymer network composition.

It is yet another object of the present invention to provide reversibly gelling polymer networks which are composed of biocompatible polymers.

The objects of the invention are achieved with a viscosifying polymer network containing an associating component capable of aggregating in response to an increase in temperature, and a solvophilic component which is linked to the associating component in a solvent. The associating component may exhibit aggregation at a temperature where no macrophase separation occurs. Both the associating and/or solvophilic components may be oligomers or polymers.

As used herein, an associating component is an oligomer or polymer which will respond to a temperature change to change its degree of association and/or agglomeration. The stimulus may be temperature, and additionally, pH, ionic concentration, solvent concentration, light, magnetic field, electrical field, pressure or other triggers commonly used to trigger a responsive gel material. The aggregation is most commonly in the form of micelle formation, however, precipitation, labile crosslinking or other factors may be contemplated as within the scope of the invention.

As used herein, the solvophilic component is an oligomer or polymer which is linked to the associating component so that a copolymer network is formed. The solvophilic component may be, but is not required to be, responsive in that it may also exhibit a change in conformation, upon a change in environmental stimulus. The interaction of the solvophilic and associating components exhibits a synergistic effect, which magnifies the effect of the associating component in viscosifying and/or gelling the solution. It may also cause aggregation and/or micellation to occur under conditions which would show no apparent effect in the absence of the polymer network. By "solvophilic", as that term is used herein, it is meant a component which has an affinity for the solvent used in solvation of the polymer network.

In the absence of the solvophilic component, the associating component may or may not show a change in viscosity in response to a change in temperature. However, if it does show a response in the absence of the solvophilic component, that response is

qualitatively or quantitatively different. That is, the response is amplified or altered in the presence of the solvophilic components.

The viscosifying polymer network is formed by solvation of the linked associating and solvophilic components. Since a gel comprises a three-dimensional polymeric network containing a solvent, the liquid component makes up the responsive viscosifying polymer network.

For commercial applications, the composition may of course include additional elements, such as are needed for the commercial purpose of the composition. These additives may have no beneficial or detrimental effect on the polymer network (i.e., inert additives) but have a beneficial aspect for the particular commercial application or formulation. These additives may have some detrimental effect to the polymer network (i.e., compromising additives) but have a beneficial effect on the particular commercial application or formulation. As such, polymer networks may represent a compromise between the requirements of the application or formulation and the requirements of the polymer network.

The novel interaction between the constituent polymers in the responsive viscosifying polymer network permits formation of gels at very low solids content. Gelation and/or viscosification is observed in aqueous solutions having about 0.01 to 20 wt% of the associating component and about 0.01 to 20 wt% of the solvophilic component.

A typical reversibly gelling polymer network may advantageously be comprised of less than about 4 wt% of total polymer solids of which less than about 2 wt% is the associating component and less than about 2 wt% is the solvophilic component. The balance is made of the aqueous-based solvent. An exemplary associating component is a poloxamer having the formula (EO)(PO)(EO). An exemplary solvophilic component is sodium acrylate. The viscosifying polymer network is formed by polymerization of acrylic acid in the presence of the poloxamer followed by hydration and neutralization of the polyacrylic acid. The viscosity of the gel increases at least ten-fold with an increase in temperature of about 5°C.

By "gelation", as that term is used herein, it is meant a drastic increase in the viscosity of the solution. Gelation is dependent on the initial viscosity of the solution, but typically a viscosity increase in the range of 5- to 100-fold, and preferably 10- to 100-fold, is observed in the present systems.

By "poloxamer", as that term is used herein, it is meant a polymeric or

oligomeric structure having a general formula of $(P_1)_a(P_2)_b(P_3)_c$, where P_1 and P_2 represent two different poloxamer blocks. By way of example only, P_1 may be a poloxamer of the general formula $(CH_2CH_2O)_a$, where a is in the range of 10-50 and P_2 may be a poloxamer of the general formula, $(CHR_1CHR_2O)_b$, where R_1 may be H or an alkyl group, R_2 may be an alkyl group, and where b is in the range of 50-70. Other possible poloxamer combinations are contemplated within the scope of the invention.

Brief Description of the Drawing

The invention is described with reference to the Drawing, which is presented for the purpose of illustration and is in no way intended to be limiting, and in which:

Figure 1 is a graph of viscosity vs. temperature for a 1 wt%, 2 wt% and 3 wt% viscosifying polymer network aqueous composition of a triblock poloxamer/polyacrylic acid (1:1) at pH 7.0 measured at a shear rate of 0.44 sec^{-1} ;

Figure 2 is a graph of viscosity vs. pH for a 1 wt% viscosifying polymer network aqueous composition of a triblock poloxamer/polyacrylic acid (1:1) at pH 7.0 measured at a shear rate of 0.44 sec^{-1} ;

Figure 3 is a graph of viscosity vs. temperature for a 2 wt% viscosifying polymer network aqueous composition of a triblock poloxamer/polyacrylic acid (1:1) in sea water at pH 7.0 measured at a shear rate of 0.22 sec^{-1} ;

Figure 4 is a plot of endotherms for (a) 1 wt% Pluronic® F127 and (b) 1 wt% viscosifying polymer network aqueous composition of Pluronic® F127/polyacrylic acid (1:1);

Figure 5 is a plot of viscosity vs. temperature for (a) a 1 wt% viscosifying polymer network aqueous composition of Pluronic® F127/polyacrylic acid (1:1) and (b) a 1 wt% physical blend of Pluronic® F127/polyacrylic acid (1:1) at pH 7.0 measured at a shear rate 0.22 sec^{-1} ;

Figure 6 is a plot of viscosity vs. temperature for a 1 wt% viscosifying polymer network aqueous composition of Pluronic® F108/polyacrylic acid (1:1) at pH 7.0 measured at a shear rate 2.64 sec^{-1} with a SC4-18 spindle;

Figure 7 is a plot of endotherms for 1 wt% viscosifying polymer network composition of Pluronic® F108/polyacrylic acid (1:1);

Figure 8 is a plot of viscosity vs. temperature for a 1 wt% viscosifying polymer network aqueous composition of Pluronic® F88/polyacrylic acid (1:1) at pH 7.0 measured at a shear rate 2.64 sec^{-1} with a SC4-18 spindle;

Figure 9 is a graph of the viscosity vs. temperature effect for a viscosifying polymer network composition of 2 wt% Pluronic® P104/polyacrylic acid (1:1) in deionized water at pH 7.0 measured at shear rate of 22 sec^{-1} using a SC4-25 spindle;

Figure 10 is plot of viscosity vs. temperature for a viscosifying polymer network composition of 2 wt% Pluronic® F123/polyacrylic acid (1:1) at pH 7.0 measured at a shear rate of 22 sec^{-1} using a SC4-25 spindle;

Figure 11 is a plot of viscosity vs. temperature for 1 wt% viscosifying polymer network made of series of triblock copolymers and polyacrylic acid (1:1) in deionized water at a shear rate of 132 sec^{-1} ;

Figure 12 is plot of viscosity vs. temperature for a viscosifying polymer network composition of 2.5 wt% Pluronic® F127/polyacrylic acid (1:1) prepared in (a) deionized water and (b) 0.5M NaCl solution;

Figure 13 is plot of viscosity vs. temperature for a viscosifying polymer network composition of 2 wt% Pluronic® F127/poly(acrylic acid-co-methacrylic acid) (1:1) in deionized water at a shear rate of 22 sec^{-1} ;

Figure 14 is plot of viscosity vs. temperature for a viscosifying polymer network composition of 2.5 wt% Pluronic® F88/polyacrylic acid (1:1) in deionized water and at 5000 psi;

Figure 15 is a plot of viscosity vs. temperature for a viscosifying polymer network composition of a 2 wt% polyethyleneglycol mono(nonylphenylether)/polyacrylic acid (1:1) at pH 7.0 at a shear rate of 2.64 sec^{-1} ;

Figure 16 is a plot showing the release of hemoglobin from a polymer network composition of the invention;

Figure 17 is a plot showing the release of lysozyme from a polymer network composition of the invention;

Figure 18 is a plot showing the release of insulin from a polymer network composition of the invention;

Figure 19 is a plot showing the release of timolol from (a) a control; (b) a 2 wt% polymer network composition and (c) a 3 wt% responsive polymer network composition of the invention;

Figure 20 is a plot of viscosity vs. temperature for a polymer network composition (a) before and (b) after sterilization by autoclave;

Figure 21 is a plot of viscosity vs. temperature for a 5 wt% polymer network prepared from polyacrylamide and Pluronic F127 (1:1) after standing for 10 days;

Figure 22 is plot of viscosity vs. temperature for a polymer network composition of 5 wt% Pluronic F127/poly(acrylamide) (1:1) in deionized water at a shear rate of 2 sec^{-1} (a) after standing one day and (b) after standing six days;

Figure 23 is plot of viscosity vs. temperature for a polymer network composition of 20 wt% Pluronic® F127/poly(acrylamide) (1:1) in deionized water at a shear rate of 0.066 sec^{-1} after standing 12 days;

Figure 24 is a plot of viscosity vs. temperature for an oil-free moisturizing formulation prepared from (a) polymer network composition of the invention and (b) a conventional oil-in-water formulation;

Figure 25 is a plot of (a) viscosity v. temperature and (b) absorbance v. temperature for a 2 wt% viscosifying polymer network prepared from poly(acrylic acid) and Pluronic® F127 (1:1); and

Figure 26 is a plot of (a) viscosity v. temperature and (b) absorbance v. temperature for a 2 wt% viscosifying polymer network prepared from poly(acrylic acid) and Pluronic® L92 (1:1).

Detailed Description of the Invention

The present invention is directed to a novel reversibly gelling polymer network. The polymer network advantageously contains less than about 20 wt% polymer solids, and preferably less than about 4 wt% polymer solids and exhibits an at least five-fold increase in viscosity with an increase of temperature of about 5°C . The responsive polymer network composition according to the invention includes an associating component and a solvophilic component. The two polymer phases are linked with one another on a molecular level, typically through a direct covalent bond, although linkages through atoms or other moieties is contemplated. Exemplary concentrations of the constituent polymers, giving the widest range of viscosity changes, range from about 10 wt% to about 75 wt% for the associating component and from about 90 wt% to about 25 wt% for the solvophilic polymer.

A viscosifying polymer network of the present invention is a special type of polymer-polymer composition, in which the two or more polymer phases are covalently linked, although other associating mechanisms, such as hydrogen bonding and van der Waals force may also be present. The interacting nature of the two (or more) polymer phases provide a stable miscible composition, irrespective of the immiscibility of the constituent polymers, and unique properties. Such stability and properties may be

attributed to specific interactions of the constituent polymers.

The associating component undergoes a change in conformation in solution. One type of associating component is a temperature-sensitive aggregating polymer. A temperature-sensitive aggregating polymer undergoes conformational changes and changes to the critical micelle concentration as a function of temperature. The polymer will change from an open, non-aggregated form to a micellar, aggregated form with changes in temperature.

The solvophilic component may be a polymer which is capable of ionization with a change in ionic strength of the solution. Changes in ionic strength may be accomplished by a change in pH or by a change in salt concentration. Changes to the ionic state of the polymer causes the polymer to experience attractive (collapsing) or repulsive (expanding) forces. Ionization is not required, however, and the solvophilic component may be neutral or uncharged.

The associating component of the polymer network exhibits a reversible gelation upon exposure to a change in temperature. The solvophilic component of the polymer network may also exhibit a reversible gelation in response to one or more environmental changes. The gelation may occur in response to an indirect environmental trigger, for example, light irradiation or electric field application which generates an increase in temperature. Alternatively, gelation may be triggered by a change in pH, ionic strength or solvent composition. Responsive polymer network gel compositions which exhibit a reversible gelation at body temperature (32-37°C) and/or at physiological pH (ca. pH 7.0-7.5) are particularly preferred for certain medical and pharmaceutical uses. Responsive polymer network compositions which exhibit a reversible gelation at 70°C or above are particularly preferred for oil field applications. Yet it is within the scope of the present invention for reversible gelation to occur at much higher or lower temperatures or pHs or in response to other stimuli.

In one embodiment of the invention, the polymer network exhibits flow properties of a liquid at about room temperature, yet rapidly thicken into a gel consistency of at least about five times greater, preferably at least about 10 times greater, and even more preferably at least about 30 times and up to 100 times greater, viscosity upon exposure to the particular environmental trigger. The responsive polymer network of the present invention exhibit gelation even at very low polymer concentrations. For example, aqueous responsive polymer network compositions of about 0.5 wt% responsive component and about 0.5 wt% ionizing polymer will gel

when exposed to a critical temperature or pH. The low polymer concentration in the aqueous compositions of the present invention provide clear, colorless gels, both before and after viscosification, making them particularly well-suited for a variety of applications. In addition, very little residue is formed upon evaporation which may be important in some applications, such as administration of ophthalmic drugs to the eyes or in topically applied cosmetics. An additional advantage of the polymer network of the invention is that it remains clear and translucent above and below the critical temperature or pH.

The associating component of the present invention may be any polymer which forms aggregates as a function of temperature. The associating component typically possess regions, which are themselves sub-components of hydrophilic and hydrophilic character. The associating component may be linear or branched. As will be apparent to one skilled in the art, a nonionic surfactant, due to its hydrophilic and hydrophilic character, may be suitable for use in the invention.

Suitable associating components include poloxamers, such as block copolymers of different oxyalkylene units. At least one polyoxyalkylene unit should have associating characteristics and at least one polyoxyalkylene unit should have hydrophilic characteristics. A poloxamer of polyoxyethylene and polyoxypropylene may be used in a preferred embodiment of the invention. Another suitable responsive component includes Pluronic® poloxamer (BASF) having the general formula $(POE)_a(POP)_b(POE)_c$, where POP is polyoxypropylene and represents the associating portion of the polymer and POE is polyoxyethylene and represents the hydrophilic portion of the polymer. Pluronic® (BASF) triblock polymers are commercially available for a and c in the range of about 16 to 48 and b ranging from about 54-62. Other exemplary polyoxyalkylene polymers include alkyl poloxamers, which are a product of alcohol condensation reactions with a terminal alkyl or arylalkyl group. The alkyl group should have associating character, such as butyl, hexyl and the like. An alkyl poloxamer may have the general formula $R-(OCH_2CH_2)_nOH$, where R is a nonpolar pendant group such as alkyl and arylalkyl and the like, and n is in the range of 5-1000. A preferred alkylpoloxamer is polyethyleneglycol mono(nonylphenyl)ether. Still other exemplary responsive components may include cellulosic, cellulose ethers and guar gums which possess hydrophobic and hydrophilic regions along the polymer backbone which permit aggregation behavior. One or more associating components may be used in the responsive polymer network composition of the present invention.

Another type of solvophilic components is an ionizable polymer. These materials typically are responsive to changes in pH and/or ionic strength. The ionizable polymers of the present invention include linear, branched and/or crosslinked polymers. Of particular interest are carboxyvinyl polymers of monomers such as acrylic acid, methacrylic acid, ethacrylic acid, phenyl acrylic acid, pentenoic acid and the like. Polyacrylic acid is a preferred carboxyvinyl polymer. One or more poly(carboxyvinyl) polymers may be used in the responsive polymer network compositions of the present invention. Acrylamides or substituted acrylamides are also preferred embodiments. Copolymers, such as by way of example only, copolymers of acrylic acid and methacrylic acid, are also contemplated. Naturally occurring polymers such as chitosan or hyaluronic acids are also possible as solvophilic polymers since they are capable of forming an ionized network as polymers or copolymers of other solvophilic polymers.

As is clear from the description of the invention and from the Examples set forth below, covalent cross-linking within an particular polymer component of the responsive polymer network is not required in order to observe gelation at low solids contents, such as less than 20 wt% or preferably less than about 10 wt%, or more preferably less than about 5 wt% or most preferably less than about 2.5 wt%. This is in contrast to Joshi *et al.* (U.S. Patent No. 5,252,318) which discloses the use of at least one crosslinked polymer in the formation of their reversibly viscosifying blends.

The reversibly gelling responsive polymer networks compositions of the present invention are highly stable and do not exhibit any phase separation upon standing or upon repeated cycling between a liquid and a gel state. Samples have stood at room temperature for more than three months without any noticeable decomposition, clouding, phase separation or degradation of gelation properties. This is in direct contrast to polymer blends and aqueous mixed polymer solutions, where phase stability and phase separation is a problem, particularly where the constituent polymers are immiscible in one another.

The functioning of a component as the associating or solvophilic component may be dependent upon the specific environmental trigger being considered. For example, in the poly(acrylic acid)/EO/PO/EO system, when temperature is the trigger, EO/PO/EO is the associating component, however at pH of 2-5, where the polymer is completely protonated, the poly(acrylic acid) may be the associating component.

Exemplary of the dramatic increase in viscosity and of the gelation of the responsive polymer network aqueous compositions of the invention with a change in

temperature are the aqueous responsive polymer network compositions shown in Fig. 1. Fig. 1 is a graph of viscosity vs. temperature for 1%, 2% and 3% aqueous responsive polymer network compositions comprising a poloxamer of the general formula (POP)(POE)(POP) and polyacrylic acid (1:1), which has been hydrated and neutralized.

5 The viscosity measurements were taken on a Brookfield viscometer at a shear rate of 0.44 sec^{-1} at pH 7.0. All solutions had an initial viscosity of about 1080 cP and exhibited a dramatic increase in viscosity to gel point at about 35°C . Final viscosities were approximately 33,000 cP, 100,000 cP and 155,000 cP for the 1 wt%, 2 wt% and 3 wt% compositions, respectively. This represents viscosity increases of about 30-, 90- and

10 140-fold, respectively.

Exemplary of the dramatic increase in viscosity and of the gelation of the responsive polymer network aqueous compositions of the invention with a change in pH are the aqueous responsive polymer network compositions shown in Fig. 2. Fig. 2 is a graph of viscosity vs. pH for a responsive polymer network composition comprising

15 1 wt% poloxamer/polyacrylic acid (1:1), hydrated and neutralized, taken on a Brookfield viscometer at a shear rate of 0.11 sec^{-1} at 37°C . The solutions had an initial viscosity of about 15 cP and exhibited a dramatic increase in viscosity to gel point at about pH 5.0. Final viscosities was approximately 3000 cP, which represented a viscosity increase of about 200-fold.

20 Another possible application of the observed viscosifying phenomenon is illustrated in Fig. 3 where the viscosifying effect of temperature is shown in a 2 wt% responsive polymer network composition comprising a poloxamer/polyacrylic acid in sea water. Sea water is represented by a synthetic formulation (NaCl , 23.84 g/l; CaCl_2 , 0.93 g/l; $\text{MgCl}_2 \cdot 6\text{H}_2\text{O}$, 10.76 g/l; Na_2SO_4 , 4.29 g/l; NaHCO_3 , 0.205 g/l) in water. A

25 viscosifying effect is observed at temperatures higher than 70°C which is relevant for oil field applications.

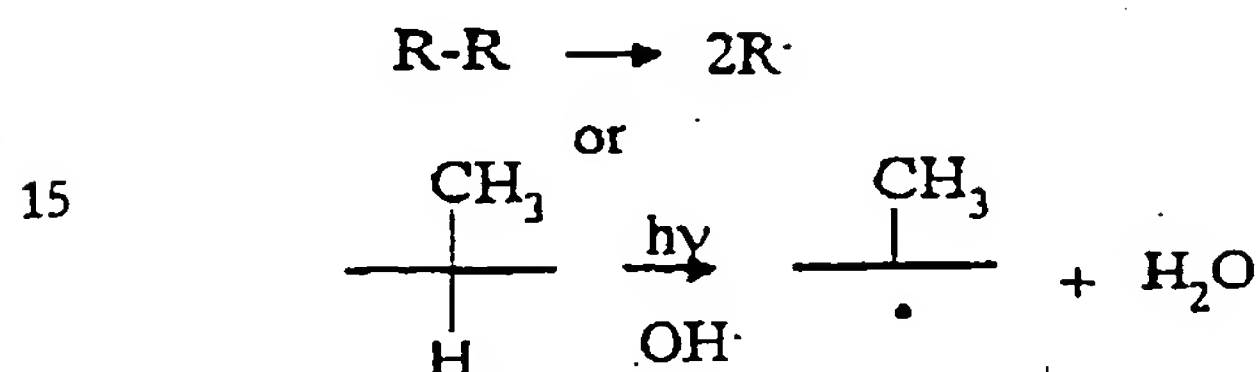
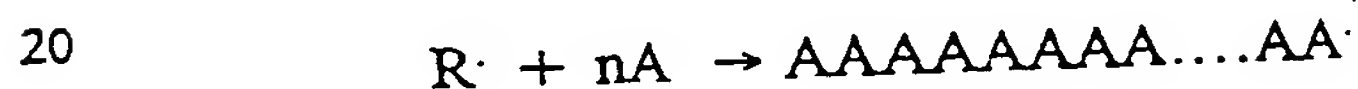
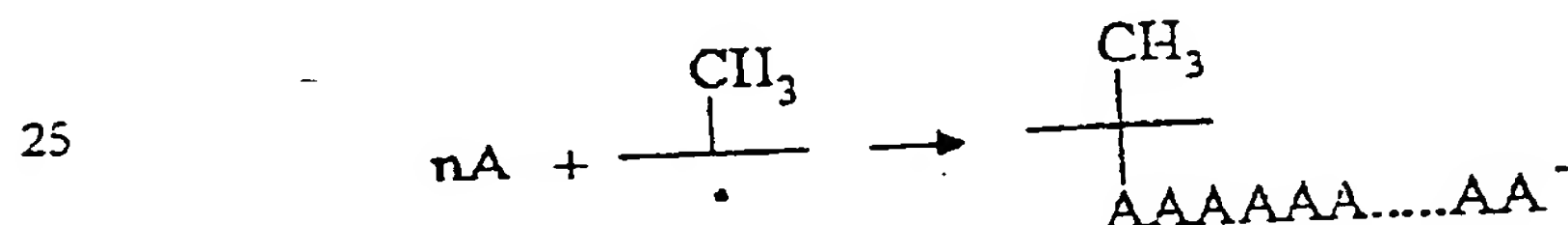
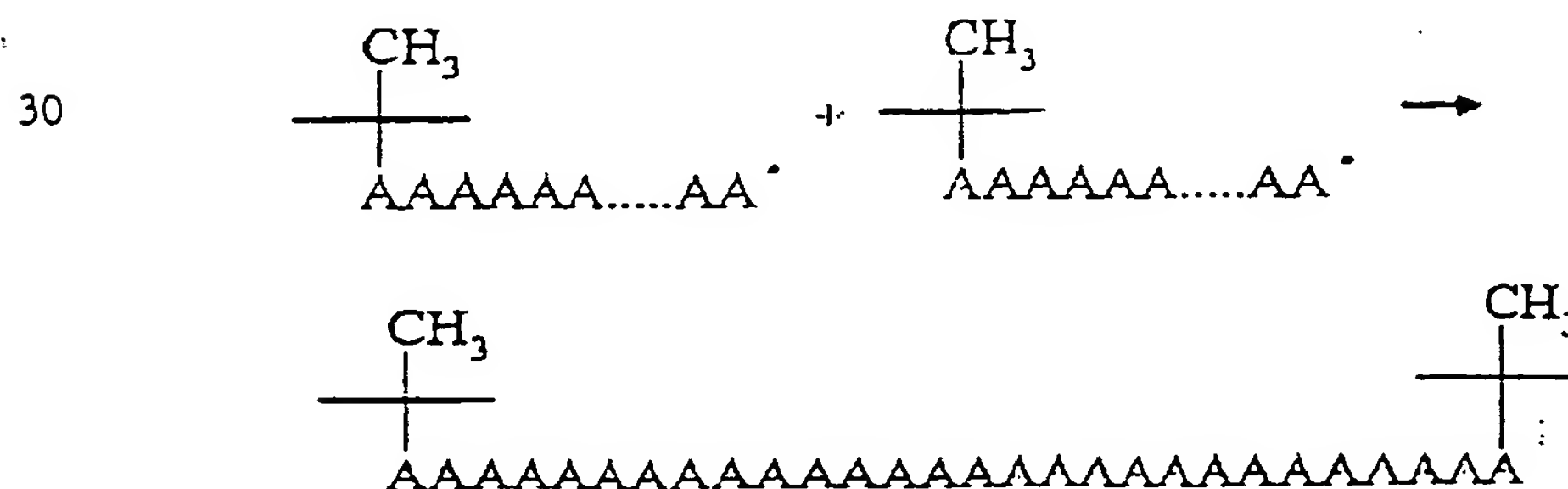
The responsive polymer network of the invention preferably is prepared by initiation of polymerization of one component, i.e., the solvophilic component, of the polymer network in the presence of the fully formed second component, i.e., the

30 associating component. A general method of making the responsive polymer network compositions generally involves solubilization of the associating component in a monomer capable or a concentrated monomer solution of forming a solvophilic component. The monomer is then polymerized to the solvophilic component. Polymerization may be accomplished by addition of a polymerization initiator or by

irradiation techniques. The initiator may be a free radical initiator, such as chemical free radical initiators and uv or gamma radiation initiators. During the polymerization, the fully formed associating component is linked to or grafted onto the developing polymer chain of the first solvophilic component. Alternatively, the terminal end of the associating and/or the solvophilic component may contain a reactive moiety, which is capable of reacting with and linking to the respective end of the complementary polymer component.

Copolymerizations may take place by proton abstraction from a secondary or tertiary carbon upon free radical formation or γ -irradiation. The copolymerizations proceeds *via* the following scheme:

SCHEME 1

Initiation:Polymerization:Graft propagation:Crosslinking:

Reactions in Scheme 1 are exemplified by propylene oxide residue, but they are equally applicable to other alkylene oxides. Note that reaction (3) in presence of vinyl monomers (typically, acrylic acid) leads to the grafting of growing poly(acrylic acid) chain onto the polyether backbone with the possibility of crosslinking, resulting in the appearance of a "classical" three-dimensional gel structure. These gel structures may form aggregates, which scatter light even at very low concentrations far below gelation temperatures.

Due to the random nature of the proton abstraction process, the grafting of the associating component onto the growing solvophilic chain is random. The degree of grafting may be adjusted by selection of the alkylene oxide (ease of free radical formation) and the quantity and type of free radical initiation used.

Although not intended to be bound to a particular mode of operation, it is believed that several factors contribute to this unique and previously unreported stability of responsive polymer networks. The polyoxyalkylene chains such as those of poloxamer polymers are known to be substantially unfolded and free-flowing at temperatures below a critical temperature of gelling. Above this temperature, the polyoxyalkylene chains have been demonstrated to form agglomerations due to the temperature-dependent association of the associating component of the polymer. See, Atwood *et al. Intl. J. Pharm.* 26:25-333 (1985), herein incorporated by reference. The polymer chains fold in on themselves due to associating interactions among associating chain blocks.

The polymer morphology of the solvophilic polymer imparts stability to the polymer network. The water-soluble solvophilic component improves the stability of the polymer network in aqueous solution, and discourages phase separation. In addition, linkage of the solvophilic and associating components increases the effective size and molecular weight of the polymer network. This amplifies the aggregation effect of the associating component.

Adachi *et al.*, which is incorporated herein by reference, report that the polymerization of acrylic acid in the presence of dilute polyoxyethylene solution resulted in an interpolymer network having a ladder-like structure in which each oxyethylene residue forms a hydrogen bond with an acrylic acid residue. Thus, template-formed polyacrylic acids of this type may contribute to the bonding observed in these new responsive polymer networks.

The properties of the responsive polymer network gel composition may be

modified by varying the components and/or the microstructure of the polymer network. For example, use of different polymerization initiators in the formation of the constituent structural component of the responsive polymer network gel was found to decrease the temperature for onset of viscosity by 5°C (see, Example 12). Also, different responsive components have been found to exhibit different reversible gelation temperatures. For example, see Examples 18-19. In addition, solvation of a responsive polymer network in a 0.5 M NaCl solution (as compared to distilled water) will result in a 10°C decrease in the temperature of gelation. Thus, the ionic strength of the aqueous solution may be used to modify the properties of the composition (see, Example 8).

Examples of thermothickening polymer systems are in the prior art; however, these systems typically operate at much higher polymer concentrations, exhibit cloud point transitions or require a complicated multistep solution synthesis. These include PEO-PPO-PEO block copolymers (Alexandritis, *et al. Colloids Surf.*, 96:1 (1995)) and other block- and graft-copolymers, such as PEO-PPO-PEO block copolymers-g-polyacrylamide (de Vos, *et al. Polymer*, 35:2644 (1994)), and PEO-g-poly(acrylic acid) (Hourdet, *et al. Polymer*, 35:2624 (1994); L'Allouret, *et al. Colloid Polym. Sci.*, 273:1163 (1995)).

Thermoassociation is attributed to aggregation of the corresponding grafts or blocks into relative associating microdomains which effectively crosslink adjacent polymer chains. Thermodynamically, aggregation results from a balance between hydrogen bonding, electrostatic interactions, and associating effects in aqueous systems. Specific orientations of water that arise upon polymer dissolution lead to increasingly unfavorable entropic (ΔS) contributions to the free energy of mixing as the temperature is raised. This tendency overcomes the favorable enthalpy (ΔH) changes due to the formation of hydrogen bonds between polymer and solvent. Let us imagine a polymer chain that consists of different segments (blocks), such that upon dissolution in, say, water, not only segment-segment contacts exist, but also segment-solvent and solvent-solvent contacts. The energy change (ΔG) per contact when we replace two segment-solvent contacts (E_{12}) and form a segment-segment (E_{11}) and a solvent-solvent (E_{22}) contact, is (Silverberg, A. *Adv. Chem. Ser.*, 1989, 223, 1),

$$\Delta G = E_{11} + E_{22} - 2E_{12}.$$

The Flory-Huggins parameter (χ) related to ΔG as follows (Flory *J. Chem. Phys.* 17:303 (1949),

$$\chi = \text{const} \times (-\Delta G/K_b T),$$

where K_b is the Boltzmann constant and T is absolute temperature (K). In the case of good solubility, $\Delta G < 0$ and $\chi < 1/2$. Phase separation starts to occur when

$$\chi \geq 1/2 [1/(1 + N^{1/2})],$$

5 where N is the size of the polymer chain.

The strong segment-segment contacts (which are needed to form associating crosslinks) require negative E_{11} values that are large in absolute terms (because ΔG must be negative; see eqn.(1)). These large values, however, lead to a very large $\chi > 1/2$, which in turn makes the polymer insoluble, resulting in conflicting requirements. Thus, in order for a polymeric system to form a reversibly viscosifying gel, it is desirably a copolymer. An associating segment that interacts very strongly with itself will form temporary crosslinks, whereas the remainder of the chain composed of a soluble segment will permit the system to stay in the solution. This is in contrast to polymer networks in which phase separation of the entire polymeric system occurs. Phase separation can present itself as cloudiness at a temperature known as LCST.

However, in a polymeric chain where associating, self-aggregating segment is a minor component and the solvophilic chain is very long, soluble aggregation occurs preferably over phase separation (i.e., precipitation or clouding). In such a system, despite the large E_{11} due to the minor associating segment, E_{12} due to interactions between water and large hydrophilic segment will overwhelm the E_{11} , thus rendering $\chi < 1/2$. No cloudiness will be observed.

The above conclusion is supported by the observation of thermothickening behavior of the two different polymer networks systems. Pluronic F127, a triblock copolymer with a minor hydrophobic component (MW of the poly(propylene oxide) (hydrophobic) section of the block copolymer is 3600, weight percentage of ethylene oxide in the copolymer is 70%, nominal total molecular weight is 12,600), exhibits no cloudiness is observed while the system gels (Figs. 25(a) and (b)). In contrast, Pluornic L-92, a triblock copolymer with a relatively major hydrophobic component (MW of the poly(propylene oxide) section of the block copolymer is 2700, weight percentage of ethylene oxide in the copolymer is only 20%, nominal total molecular weight is 3650), a very marked cloudiness is observed that is followed by gelation (Figs. 26(a) and (b)).

To further confirm the difference between aggregation phenomena in relatively "hydrophilic" polymer networks based upon Pluronic® F127 and LCST in this system, the following experiment was conducted. Absorbance of a suspension of viscosifying

polymer network (2 w% 1:1 Pluronic 127: poly(acrylic acid) in water, pH 7.0) at 500 nm was measured to be 0.0723 within the range of 3-80° C. The suspension was then placed in a vial, heated up in a microwave, gently opened up and its temperature and absorbance were immediately measured. Substantial cloudiness was observed only when
 5 the temperature exceeded 100° C. Absorbance of the suspension at 500 nm ($T > 100^{\circ}$ C) was measured to be 0.1385. Upon cooling, the cloudiness quickly disappeared. The thermothickening behavior of the suspension then was measured and the curve was essentially identical to the one shown in Fig. 25(a). Thus gelation and LCST in this system were observed to be different by ca. 70° C.

10 It has been demonstrated that the viscosifying polymer networks of the present invention demonstrate gelation at concentrations much lower than those needed for the corresponding Pluronic system to gel. However, differential scanning calorimetry (DSC) measurements demonstrated that aggregation phenomena associated with thermothickening are thermodynamically identical in both systems.

15 It is generally accepted that, in low concentrations and temperatures of poloxamer solutions, there exists an equilibrium between monomers, micelles, and micellar aggregates (Brown *et al.* *J. Phys. Chem.* 95:1850 (1991)). At low concentrations, the apparent micellar radius increases with increasing temperature. As concentration increases, aggregates grow into asymmetric particles eventually resulting in a solidlike gel
 20 that is usually observed at defined temperatures. The viscosifying polymer network of the present invention, however, does not require a significant formation of poloxamer aggregates before viscosification occurs.

Consider what addition of a gel particle into a suspension will do. For simplicity, assume the liquid to be Newtonian (it is, in fact, non-Newtonian which
 25 should show an even greater effect). When a gel particle is added to the solution, the Einstein equation can be written in the form (Ball, *et al.* *J. Phys. Chem. Liquids* 9:99 (1980),

$$d\eta = \text{const}(\eta d\phi),$$

where $d\eta$ is the increment of viscosity on the addition of a small increment of phase
 30 volume $d\phi$ to a suspension viscosity η .

When a gel particle is added to a suspension where polymer chains substantially overlap, it will require more space than its volume $d\phi$ because of the packing difficulties. Accounting for the crowding effect yields,

$$\eta = \eta_1(1-K\phi)^{-\text{const}/K}.$$

When $\phi = 1/K$, the viscosity becomes infinite. Thus, only a few gel particles are needed in the present viscosifying polymer network in order to significantly viscosify it over a poloxamer solution, such a Pluronic, lacking such particles. This effect is magnified by bridging gel particles with adjacent hydrophobic and hydrophilic components of the polymer network.

Thermogelation has been observed in hydrophobe-modified poly(n-alkylacrylamides) (Schulz, Kaladas *et al.*), polysaccharides (Jauregui *et al.*), POP-POE block copolymers (Alexandritis *et al.*) and other systems. None of these systems, however, shows useful pH-responsiveness in a wide range of temperatures. Even graft copolymers described by Hoffmann and Chen (WO 95/24430) exhibit a LCST and therefore show a cloud point in connection with viscosification. Such systems are limited to dually responsive polymers which exhibit phase separation of the entire system.

Fig. 4 shows endotherms of (a) 1% Pluronic® F127 and (b) 1% responsive polymer network (Pluronic® F127/polyacrylic acid 1:1) obtained using a MCS Differential Scanning Calorimetry System (Microcal, Inc.) by heating samples with the rate of 15 centigrade/hour. Pluronic® F127 is a triblock polymer made up of ethylene oxide (EO) and propylene oxide (PO) blocks and having the general formula (EO)(PO)(EO), where 70 wt% of the polymer is EO. Broad or sharp endothermic peaks are seen at characteristic temperature of 29°C which coincides with the onset of gelation in the responsive polymer network composition (see, Fig. 1). The peaks are measured to have enthalpy value of 1.26 cal/g. This enthalpy falls within the range reported for Pluronic solutions (see, for instance, Wanka *et al.*, *Colloid&Polymer Science*, 1990, 268, 101, herein incorporated by reference).

The aforementioned thermal behavior of associating polymer networks suggests that the observed increase of viscosity at around 30 °C is due to aggregation of poloxamer molecules at this temperature which, because of covalent bonding (and possibly hydrogen bonding and/or template formation) with polyacrylic acid or polyacrylate molecules, serve as cross-links in viscous gel-like structures of interactive polymer networks. Thus, nonionic surfactants should be well suited to the associating polymer network compositions of the present invention because of their aggregate- and micelle-forming capabilities in water.

A general method of making the responsive polymer network compositions of the present invention comprises solubilization of the associating component in a

monomer capable of forming a solvophilic component or formation of a melt of the component materials. Solvophilic components suitable for use in the method are those which exhibit expansion and contraction in response to a change in ionic strength. The monomer is polymerized to the solvophilic component. Polymerization may be accomplished by addition of a polymerization initiator or by irradiation techniques. The initiator may be a free radical initiator, such as chemical free radical initiators and uv or gamma radiation initiators. Conventional free radical initiators may be used according to the invention, including, but in no way limited to ammonium persulfate, benzoin ethyl ether, 1,2'-azobis(2,4-dimethylpentanitrile) (Vazo 52) and azobisisobutyronitrile (AIBN). Initiation may also be accomplished using cationic or ionic initiators. Many variations of this methods will be apparent to one skilled in the art and are contemplated as within the scope of the invention. For example, the solvophilic component may be dissolved in a monomer/water mixture instead of pure monomer. This may be particularly useful in instances where the temperature-sensitive aggregating monomer does not solubilize well in the monomer or in instances where the monomer of the solvophilic component is a solid. It may be desirable to remove unreacted monomer from the resultant responsive polymer network. This may be accomplished using conventional techniques, such as, by way of example, dialysis.

Reverse phase polymerization may be used to prepare responsive polymer network beads by dispersion of the solvophilic component/ionizable monomer mixture in a nonpolar solvent such as heptane. The aggregating polymer/monomer solution is dispersed with agitation in a nonpolar solvent, such as heptane or hexane, in order to suspend droplets of the solution. Polymerization of the monomer is initiated by conventional means (i.e., addition of a initiator or irradiation) in order to polymerize the monomer and form responsive polymer network beads. See, WO 96/02577 and entitled "Useful Responsive Polymer Gel Beads" for further information on the preparation of polymer gel beads, herein incorporated by reference. Such a method may be particularly desirable to provide a heat sink for the heat generated in the exothermic polymerization reaction.

Those skilled in the art will appreciate that the polymer network compositions of the present invention may be utilized for a wide variety of pharmaceutical applications. To prepare an aqueous drug delivery system, according to the teachings of the present invention an effective amount of the desired pharmaceutical agent is incorporated into the aqueous responsive polymer network composition of the present

invention. Preferably the selected compound is soluble in water which will readily lend itself to a homogeneous dispersion through out the responsive polymer network composition. It is also preferred that the compound is nonreactive with the responsive polymer network composition. For materials which are not soluble with the responsive polymer network composition, it is also within the scope of the invention to disperse or suspend powders throughout the responsive polymer network composition. It will also be appreciated that many applications will require a sterile environment. It is contemplated as within the scope of the invention that the aqueous responsive polymer network compositions of the present invention may be prepared under sterile conditions. An additional feature of the interacting polymer gels of the invention is that they may be prepared from constituent polymers that have known accepted toxicological profiles. Thus, the interacting polymer gel may be prepared from polymers which already have FDA-approval.

Exemplary drugs or therapeutics delivery systems which may be administered using the aqueous responsive polymer network compositions of the invention include, but are in no way limited to, mucosal therapies, such as esophageal, otic, rectal, buccal oral, vaginal, and urological applications; topical therapies, such as wound care, skin care and teat dips; and intravenous/subcutaneous therapies, such as intramuscular, intrabone (e.g., joints), spinal and subcutaneous therapies, tissue supplementation, adhesion prevention and parenteral drug delivery. It will be appreciated that the ionic nature of the "structural component" component of the responsive polymer network provides an adhesive interaction with mucosal tissue.

The biologically active compounds that may be loaded into the polymer networks of the present invention are any substance having biological activity, including proteins, polypeptides, polynucleotides, nucleoproteins, polysaccharides, glycoproteins, lipoproteins, and synthetic and biologically engineered analogs thereof.

Examples of biologically active compounds that might be utilized in a delivery application of the invention include literally any hydrophilic or hydrophobic biologically active compound. Preferably, though not necessarily, the drug is one that has already been deemed safe and effective for use by the appropriate governmental agency or body. For example, drugs for human use listed by the FDA under 21 C.F.R. 330.5, 331 through 361; 440-460; drugs for veterinary use listed by the FDA under 21 C.F.R. 500-582, incorporated herein by reference, are all considered acceptable for use in the present novel polymer networks.

Drugs that are not themselves liquid at body temperature can be incorporated into polymers, particularly gels. Moreover, peptides and proteins which may normally be lysed by tissue-activated enzymes such as peptidases, can be passively protected in gels as well. See, Gehrke et al. *Proceed. Intern. Symp. Control. Rel. Bioact. Mater.*, 22:145
5 (1995).

The term "biologically active compound" includes pharmacologically active substances that produce a local or systemic effect in animals, plants, or viruses. The term thus means any substance intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease or in the enhancement of desirable physical or mental
10 development and conditions in an animal, plant, or virus. The term "animal" used herein is taken to mean mammals, such as primates, including humans, sheep, horses, cattle, pigs, dogs, cats, rats, mice; birds; reptiles; fish; insects; arachnids; protists (e.g. protozoa); and prokaryotic bacteria. The term "plant" means higher plants (angiosperms, gymnosperms), fungi, and prokaryotic blue-green "algae" (i.e.
15 cyanobacteria).

The pharmaceutically active compound may be any substance having biological activity, including proteins, polypeptides, polynucleotides, nucleoproteins, polysaccharides, glycoproteins, lipoproteins, and synthetic and biologically engineered analogs thereof. The term "protein" is art-recognized and for purposes of this invention
20 also encompasses peptides. The proteins or peptides may be any biologically active protein or peptide, naturally occurring or synthetic.

Examples of proteins include antibodies, enzymes, steroids, growth hormone and growth hormone-releasing hormone, gonadotropin-releasing hormone, and its agonist and antagonist analogues, somatostatin and its analogues, gonadotropins such as
25 luteinizing hormone and follicle-stimulating hormone, peptide-T, thyrocalcitonin, parathyroid hormone, glucagon, vasopressin, oxytocin, angiotensin I and II, bradykinin, kallidin, adrenocorticotrophic hormone, thyroid stimulating hormone, insulin, glucagon and the numerous analogues and congeners of the foregoing molecules.

Classes of pharmaceutically active compounds which can be loaded into
30 responsive polymer network compositions of the invention include, but are not limited to, anti-AIDS substances, anti-cancer substances, antibiotics, immunosuppressants (e.g. cyclosporine) anti-viral substances, enzyme inhibitors, neurotoxins, opioids, hypnotics, antihistamines, lubricants tranquilizers, anti-convulsants, muscle relaxants and anti-Parkinson substances, anti-spasmodics and muscle contractants, miotics and anti-

cholinergics, anti-glaucoma compounds, anti-parasite and/or anti-protozoal compounds, anti-hypertensives, analgesics, anti-pyretics and anti-inflammatory agents such as NSAIDs, local anesthetics, ophthalmics, prostaglandins, anti-depressants, anti-psychotic substances, anti-emetics, imaging agents, specific targeting agents, neurotransmitters, proteins, cell response modifiers, and vaccines.

A more complete listing of classes of compounds suitable for loading into polymers using the present methods may be found in the *Pharmazeutische Wirkstoffe* (Von Kleemann et al. (eds) Stuttgart/New York, 1987, incorporated herein by reference). Examples of particular pharmaceutically active substances are presented below:

10. Anti-AIDS substances are substances used to treat or prevent Autoimmune Deficiency Syndrome (AIDS). Examples of such substances include CD4, 3'-azido-3'-deoxythymidine (AZT), 9-(2-hydroxyethoxymethyl)-guanine acyclovir(), phosphonoformic acid, 1-adamantanamine, peptide T, and 2',3' dideoxycytidine.

Anti-cancer substances are substances used to treat or prevent cancer. Examples of such substances include methotrexate, cisplatin, prednisone, hydroxyprogesterone, medroxyprogesterone acetate, megestrol acetate, diethylstilbestrol, testosterone propionate, fluoxymesterone, vinblastine, vincristine, vindesine, daunorubicin, doxorubicin, hydroxyurea, procarbazine, aminoglutethimide, mechlorethamine, cyclophosphamide, melphalan, uracil mustard, chlorambucil, busulfan, carmustine, 20 lomusline, dacarbazine (DTIC: dimethyltriazenomidazolecarboxamide), methotrexate, fluorouracil, 5-fluorouracil, cytarabine, cytosine arabinoside, mercaptopurine, 6-mercaptopurine, thioguanine.

Antibiotics are art recognized and are substances which inhibit the growth of or kill microorganisms. Antibiotics can be produced synthetically or by microorganisms. Examples of antibiotics include penicillin, tetracycline, chloramphenicol, minocycline, doxycycline, vanomycin, bacitracin, kanamycin, neomycin, gentamycin, erythromycin and cephalosporins.

Anti-viral agents are substances capable of destroying or suppressing the replication of viruses. Examples of anti-viral agents include a-methyl-P-adamantane methylamine, 1,-D-ribofuranosyl-1,2,4-triazole-3 carboxamide, 30 9-[2-hydroxy-ethoxy]methylguanine, adamantanamine, 5-iodo-2'-deoxyuridine, trifluorothymidine, interferon, and adenine arabinoside.

Enzyme inhibitors are substances which inhibit an enzymatic reaction. Examples of enzyme inhibitors include edrophonium chloride, N-methylphysostigmine,

neostigmine bromide, physostigmine sulfate, tacrine HCl, tacrine, 1-hydroxy maleate, iodotubercidin, p-bromotetramisole, 10-(alpha-diethylaminopropionyl)- phenothiazine hydrochloride, calmidazolium chloride, hemicholinium-3, 3,5-dinitrocatechol, diacylglycerol kinase inhibitor I, diacylglycerol kinase inhibitor II,

5 3-phenylpropargylamine, N⁶-monomethyl-L-arginine acetate, carbidopa, 3-hydroxybenzylhydrazine HCl, hydralazine HCl, clorgyline HCl, deprenyl HCl, L(-), deprenyl HCl, D(+)-, hydroxylamine HCl, iproniazid phosphate, 6-MeO-tetrahydro-9H-pyrido-indole, nialamide, pargyline HCl, quinacrine HCl, semicarbazide HCl, tranylcypromine HCl, N,N-diethylaminoethyl-2,2-diphenylvalerate

10 hydrochloride, 3-isobutyl-1-methylxanthine, papaverine HCl, indomethacin, 2-cyclooctyl-2-hydroxyethylamine hydrochloride, 2,3-dichloro-a-methylbenzylamine (DCMB), 8,9-dichloro-2,3,4,5-tetrahydro-1H-2-benzazepine hydrochloride, p-aminogluthethimide, p-aminogluthethimide tartrate, R(+)-, p-aminogluthethimide tartrate, S(-)-, 3-iodotyrosine, alpha-methyltyrosine, L-, alpha-methyltyrosine, D L-,

15 acetazolamide, dichlorphenamide, 6-hydroxy-2-benzothiazolesulfonamide, and allopurinol.

Neurotoxins are substances which have a toxic effect on the nervous system, e.g. nerve cells. Neurotoxins include adrenergic neurotoxins, cholinergic neurotoxins, dopaminergic neurotoxins, and other neurotoxins. Examples of adrenergic neurotoxins

20 include N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine hydrochloride. Examples of cholinergic neurotoxins include acetylcholine mustard hydrochloride. Examples of dopaminergic neurotoxins include 6-hydroxydopamine HBr, 1-methyl-4-(2-methylphenyl)-1,2,3,6-tetrahydro-pyridine hydrochloride, 1-methyl-4-phenyl-2,3-dihydropyridinium perchlorate, N-methyl-4-phenyl-1,2,5,6-

25 tetrahydropyridine HCl, 1-methyl-4-phenylpyridinium iodide.

Opioids are substances having opiate like effects that are not derived from opium. Opioids include opioid agonists and opioid antagonists. Opioid agonists include codeine sulfate, fentanyl citrate, hydrocodone bitartrate, looperamide HCl, morphine sulfate, noscapine, norcodeine, normorphine, thebaine. Opioid antagonists include

30 nor-binaltorphimine HCl, buprenorphine, chlornaltrexamine 2HCl, funaltrexamine HCl, nalbuphine HCl, nalorphine HCl, naloxone HCl, naloxonazine, naltrexone HCl, and naltrindole HCl.

Hypnotics are substances which produce a hypnotic effect. Hypnotics include pentobarbital sodium, phenobarbital, secobarbital, thiopental and mixtures, thereof,

heterocyclic hypnotics, dioxopiperidines, glutarimides, diethyl isovaleramide, a-bromoisovaleryl urea, urethanes and disulfanes.

5 Antihistamines are substances which competitively inhibit the effects of histamines. Examples include pyrilamine, chlorpheniramine, tetrahydrazoline, and the like.

Lubricants are substances that increase the lubricity of the environment into which they are delivered. Examples of biologically active lubricants include water and saline.

10 Tranquilizers are substances which provide a tranquilizing effect. Examples of tranquilizers include chlorpromazine, promazine, fluphenzaine, reserpine, deserpidine, and meprobamate.

Anti-convulsants are substances which have an effect of preventing, reducing, or eliminating convulsions. Examples of such agents include primidone, phenytoin, valproate, Chk and ethosuximide.

15 Muscle relaxants and anti-Parkinson agents are agents which relax muscles or reduce or eliminate symptoms associated with Parkinson's disease. Examples of such agents include mephenesin, methocarbomal, cyclobenzaprine hydrochloride, trihexylphenidyl hydrochloride, levodopa/carbidopa, and biperiden.

20 Anti-spasmodics and muscle contractants are substances capable of preventing or relieving muscle spasms or contractions. Examples of such agents include atropine, scopolamine, oxyphenonium, and papaverine.

Miotics and anti-cholinergics are compounds which cause bronchodilation. Examples include echothiophate, pilocarpine, physostigmine salicylate, diisopropylfluorophosphate, epinephrine, neostigmine, carbachol, methacholine, 25 bethanechol, and the like.

Anti-glaucoma compounds include betaxalol, pilocarpine, timolol, timolol salts, and combinations of timolol, and/or its salts, with pilocarpine.

Anti-parasitic, -protozoal and -fungals include ivermectin, pyrimethamine, trisulfapyrimidine, clindamycin, amphotericin B, nystatin, flucytosine, natamycin, and 30 miconazole.

Anti-hypertensives are substances capable of counteracting high blood pressure. Examples of such substances include alpha-methyldopa and the pivaloyloxyethyl ester of alpha-methyldopa.

Analgesics are substances capable of preventing, reducing, or relieving pain.

Examples of analgesics include morphine sulfate, codeine sulfate, meperidine, and nalorphine.

5 Anti-pyretics are substances capable of relieving or reducing fever and anti-inflammatory agents are substances capable of counteracting or suppressing inflammation. Examples of such agents include aspirin (salicylic acid), indomethacin, sodium indomethacin trihydrate, salicylamide, naproxen, colchicine, fenoprofen, sulindac, diflunisal, diclofenac, indoprofen and sodium salicylamide.

10 Local anesthetics are substances which have an anesthetic effect in a localized region. Examples of such anesthetics include procaine, lidocain, tetracaine and dibucaine.

Ophthalmics include diagnostic agents such as sodium fluorescein, rose bengal, methacholine, adrenaline, cocaine, and atropine. Ophthalmic surgical additives include alpha-chymotrypsin and hyaluronidase.

15 Prostaglandins are art recognized and are a class of naturally occurring chemically related, long-chain hydroxy fatty acids that have a variety of biological effects.

Anti-depressants are substances capable of preventing or relieving depression. Examples of anti-depressants include imipramine, amitriptyline, nortriptyline, protriptyline, desipramine, amoxapine, doxepin, maprotiline, tranylcypromine, phenelzine, and isocarboxazide.

Anti-psychotic substances are substances which modify psychotic behavior. Examples of such agents include phenothiazines, butyrophenones and thioxanthenes.

Anti-emetics are substances which prevent or alleviate nausea or vomiting. An example of such a substance includes dramamine.

25 Imaging agents are agents capable of imaging a desired site, e.g. tumor, *in vivo*. Examples of imaging agents include substances having a label which is detectable *in vivo*, e.g. antibodies attached to fluorescent labels. The term antibody includes whole antibodies or fragments thereof.

30 Specific targeting agents include agents capable of delivering a therapeutic agent to a desired site, e.g. tumor, and providing a therapeutic effect. Examples of targeting agents include agents which can carry toxins or other agents which provide beneficial effects. The targeting agent can be an antibody linked to a toxin, e.g. ricin A or an antibody linked to a drug.

Neurotransmitters are substances which are released from a neuron on excitation

and travel to either inhibit or excite a target cell. Examples of neurotransmitters include dopamine, serotonin, γ -aminobutyric acid, norepinephrine, histamine, acetylcholine, and epinephrine.

Cell response modifiers are chemotactic factors such as platelet-derived growth factor (PDGF). Other chemotactic factors include neutrophil-activating protein, 5 monocyte chemoattractant protein, macrophage-inflammatory protein, platelet factor, platelet basic protein, and melanoma growth stimulating activity; epidermal growth factor, transforming growth factor (alpha), fibroblast growth factor, platelet-derived endothelial cell growth factor, insulin-like growth factor, nerve growth factor, and bone 10 growth/cartilage-inducing factor (alpha and beta), or other bone morphogenetic protein.

Other cell response modifiers are the interleukins, interleukin inhibitors or interleukin receptors, including interleukin 1 through interleukin 10; interferons, including alpha, beta and gamma; hematopoietic factors, including erythropoietin, granulocyte colony stimulating factor, macrophage colony stimulating factor and 15 granulocyte-macrophage colony stimulating factor; tumor necrosis factors, including alpha and beta; transforming growth factors (beta), including beta-1, beta-2, beta-3, inhibin, and activin; and bone morphogenetic proteins.

As those skilled in the art will appreciate, the foregoing list is exemplary only. Because the aqueous responsive polymer network composition of the present invention 20 is suited for application under a variety of physiological conditions, and in particular is well-suited for transmucosal applications, a wide variety of pharmaceutical agents may be incorporated into and administered from the responsive polymer network composition.

Other routes of delivery include, but are not limited to, ophthalmic, otic, nasal, buccal, sublingual, injectable, dermal, subdermal, oral, vaginal and rectal. These routes 25 benefit from the responsive polymer network being a system that has reverse viscosification, bioadhesion, and emulsification properties. In terms of ophthalmic delivery, the responsive polymer network composition may be used as a liquid vehicle at ambient temperature, and after administration to the eye, the responsive polymer network would become viscous to facilitate the delivery of actives or act as an adjuvant 30 for lubricity and humectancy. In terms of nasal delivery, the responsive polymer could be delivered as a spray to the nasal cavity which would then viscosify in place, and provide a film for coating the nasal mucosa. In terms of injectable delivery, the responsive polymer network compositions may be used as an enteric coating for tablets or as a suspension for delivery of active agents that benefit from extended release

through viscosification in the gastrointestinal tract. In terms of vaginal and rectal delivery, typical formulations exhibit viscosity decreases at body temperature and exude out of the vaginal or rectal cavity. The increase in viscosity at body temperature that the responsive polymer network exhibits will help to prevent leakage.

5 The responsive polymer network composition may be used in a variety of applications where it is desired to change the viscosity of a liquid environment. The responsive polymer network composition may be used to reversibly modify the viscosity of an article, device or composition, by incorporating an aqueous responsive polymer network composition comprised of about 0.01 to 20 wt%, and preferably about
10 0.1 to 5 wt%, of associating responsive component and about 0.01 to 20 wt%, and preferably about 0.1 to 5 wt%, of a solvophilic component capable of expansion and contraction as a function of ionic strength into the article, device or composition. By increasing temperature, the aqueous composition exhibits at least a five-fold increase in viscosity upon gelation, and by reducing temperature, the composition exhibits at least a
15 five-fold decrease in viscosity upon liquification.

The four primary characteristics of the materials introduced herein, which can be exploited for commercial applications are:

- 1) Reversible viscosification above the transition temperature.
- 2) Reversible "setting" at temperatures above the transition temperature.
- 20 3) Controlled release of loaded molecules.
- 4) Conformation to physical environment upon viscosification or formation of a semi-solid material

Reversible Viscosification: The reversible viscosification of the responsive polymer network family at elevated temperatures makes the materials ideal for a
25 magnitude of functions in several different fields. One application would be in the industrial and automotive use of oils and lubricants. Traditional lubricating products tend to thin under high temperature conditions, often to the point where they become completely ineffective in reducing friction. An oil or lubricant which contained the correct proportion of a reverse thermal gel, however, would be just as effective at high
30 temperatures as at low temperatures, as the viscosifying effect of the responsive polymer network would counteract the thinning of the other constituents of the lubricant as the temperature rose above the responsive polymer network's transition temperature. The same principle which makes the responsive polymer network's useful in this application would also make them suitable as thickening agents in other commercial products such

as paints and coatings, liquid cleaners and polishers, as well as food products, especially microwave foods, at any temperature above the transition. Cleaning products which are intended to act at high temperatures, oven cleaners in particular, would especially benefit from the addition of a reverse-thermal transition responsive polymer network, as the viscosifying effect above the transition temperature would act to thicken the solution and keep the cleaner fixed and evenly spread over the oven surface during the cleaning process. Novel products could also be developed from this principle such as a "liquid chewing gum" which could be sold, stored, and introduced into the mouth as a liquid, at which point it would viscosify and take on the properties of regular chewing gum.

Another primarily industrial use of the "thickening" of solutions containing the responsive polymer network is in emulsions. Currently emulsifiers are often negatively effected by increased temperatures. A simple example is the loss of volume and "lightness" of whipped cream upon heating. An additive with reverse thermal viscosification properties, however, would react in exactly the opposite way, increasing its ability to emulsify as it gained three-dimensional structure upon heating above its transition temperature. The ability to emulsify solutions at high temperatures would be applicable in other solutions, including paints, coatings, and waxes.

In the applications where the responsive component is a surfactant, the responsive polymer network will have the ability to act as a primary emulsifier without any (or with very little) addition of traditional surfactant. The responsive polymer network will also act as a stabilizer for oil-soluble ingredients that would conventionally need to be solubilized by oils in formulation. The associating portion of the interacting penetrating network forms domains that act as reservoirs for such materials. These two features of the material of the invention would enable it to be used as a base in a cosmetic formulation that would be non-greasy due to lack of oils, such as petrolatum and mineral oil.

The emulsification abilities of the responsive polymer network would allow a material to be maintained in a system for an indefinite period of time. The emulsification could provide a barrier around the material. An example would be a pigment or a dye in a mascara. The emulsification abilities of the responsive polymer network could also provide a controlled diffusion from the material upon activation. Two examples would be the continuous release of a fragrance in a deodorant or cologne, or the release of an active ingredient such as an antiperspirant.

The responsive polymer network's ability to viscosify with increased temperature could provide a semi-permeable or impermeable barrier. In a cosmetic formulation, this feature would provide a protective barrier or allow for a slow diffusion of other materials. The responsive polymer network may also become increasingly rigid with increasing temperature and thereby create rigidity in cosmetics.

The responsive polymer network exhibits bioadhesive characteristics. In cosmetic formulations, the responsive polymer network would adhere to the skin or hair or hold other materials to the skin or hair.

The reversible gels of the invention could also have a significant benefit in cases where one wished to maintain or establish a viscosity property in a change from a cold (e.g., refrigerated) to a heated environment. Two examples are dripless ice cream (where the gel serves to add viscosity to the ice cream as it melts) and a repair system for the Alaska pipeline (where a joint might contain a liquid version of the gel which would viscosify in the event of an oil leak to keep oil from leaking, the oil being at an elevated temperature compared to the cold Alaskan environment).

The gel could also provide a dye to indicate that something had been exposed to too low a temperature. Currently, there are products that are designed to change color and indicate when something has been exposed to too high a temperature, but this dye could indicate, for example, that a material that changes state, i.e., crystallinity, has been frozen and therefore the change of state indicated by the change of color would be important.

The material can also be useful to help introduce a gel-like material into a space where a semi-solid material would be difficult to introduce. For example, in capillary electrophoresis, it would be useful to introduce the separations material in a liquid form and then to gel it in situ, thereby greatly reducing the time required. As another example, electrical and optical wires are often protected by gels, and the gel of the present invention could help protect such wires by allowing field repair and coating in difficult to reach areas.

Finally, the ability to form a highly viscous solution reversibly may be especially useful in electrophoresis and other types of chromatography. The material could be poured into columns or plates at low temperatures, warmed above the transition to produce a matrix with separation capabilities, and then cooled after separation for easy replacement of contaminated material and recovery of products.

Setting or Binding. The second property of the responsive polymer network's,

the ability to set up with increased temperatures, can be viewed as an extension of the viscosifying effect but has somewhat different applications. In the food industry for instance, this characteristic would be useful in the manufacturing process. For example, the fast setting of the responsive polymer network could be utilized in the manufacture of hard candies where it would be useful to have the product take on more manageable handling properties quickly, before the slower process of hardening by cooling sets in. In formulations approved by the proper regulatory agencies, the responsive polymer network's could be introduced into the candy formulation in appropriate amounts to cause the candy to harden enough to be moved along in the manufacturing process long before the candy has cooled enough to become solid and non-tacky on its own. This process might also introduce further desired properties in the end-product by making the candy slower melting and longer lasting.

The same effect could also be introduced into additional industrial applications where the responsive polymer network might serve in binding, extrusion, molding, cementing, and modified coating applications. An example of the use of the responsive polymer network as a binding agent would be in ceramics. In this case, the binding agent holds together the fine particles of the ceramic object until the firing process is complete. The responsive polymer network is ideal for this application because it can be easily applied as a solution and will hold the particles in place until the object is fully fired, since it will begin to viscosify and bind particles as soon as the temperature is slightly elevated and will continue to do so even at the high temperatures involved in the firing process. The system can also serve as a thixatropes or a viscosity modifying agent below gelation temperature. In the same way, the responsive polymer network solutions could be useful for sheet and fiber extrusion as well as molding processes, as they would supply the cohesion which is necessary prior to the completion of curing. In cementing applications, the reverse thermal gelation would be useful in any instance in which it would be desirable to have the cement set up quickly. Exothermic reactions, such as cement curing, would be particularly interesting because the heat generated would cause a significant thickening of the uncured cement. Thus, the correct amount of responsive polymer network would help the cement to set even before the curing process was complete. For coatings, the responsive polymer network solutions could be used in modified setups where the coating material is mixed with the responsive polymer network solution and applied to the surface to be coated. The temperature could then be elevated above the transition temperature, firmly but

temporarily fixing the coating in place. The temperature could then be further elevated to drive off the remaining water, leaving behind the smoothly coated material. Another industrial application for the responsive polymer network family is in adhesive applications and pastes. In those instances where it is preferred that one have an adhesive which can be made to adhere and then easily reverse its properties, the responsive polymer network's could be ideal candidates. A correctly formulated solution could be designed with the needed degree of strength and adherence when the responsive polymer network sets up above its transition temperature. The adhesion could then be reversed simply by reducing the temperature below the transition.

Controlled Release. The ability to provide controlled release of relatively small molecules, previously examined in detail for personal care and pharmaceutical applications, could also be applied to the agricultural and industrial fields. For example, a "plant food" solution, applied to soil as a liquid at low temperature and allowed to viscosify at ground temperature, would provide prolonged release of nourishment to crops by significantly reducing runoff and isolating the nutrients around the roots of the plants. In industrial applications, the same principle could be exploited to provide a slow and continuous stream of any additive, slowing the rate of introduction of the additive at elevated temperatures. The release could be utilized in coating systems, cleaning systems, and manufacturing processes in which it is desirable to keep the additive in physical proximity to other materials involved in the process, without allowing the total amount of additive to become involved in the system's activities at the time it is introduced. The controlled release of materials is also very applicable to the food industries, where one could envision the use of controlled diffusion from the material above its transition temperature to provide a constant release of flavors and fragrances in the mouth. Likewise, the ability of the highly viscosified responsive polymer network to impede movement of large molecules could be utilized to produce "enzyme factories" where the enzyme is immobilized by the rigid structure, but substrate and product molecules are allowed to diffuse in and out of the matrix.

Conformation. The ability of the responsive polymer network's to conform to any shape upon formation of the semi-solid state has applications in a variety of consumer products. The reversibly gelling polymer networks could be used in a variety of footwear applications, such as in the insoles (factory or aftermarket), ankle collar, tongue, etc. to give the wearer a custom fit and to enhance comfort and support. This could be incorporated into almost any type of footwear including athletic shoes

(walking, running, cross training, basketball, tennis, golf, cleated, etc.) casual or dress shoes, slippers, sandals, hiking boots, work boots, ski boots, in line skates, ice skates, etc.

These gels can also be used to provide conformable fit and support in a variety of different protective gear and sporting goods applications such as helmets (football, baseball, hockey, bicycle, motorcycle etc.), mouthpieces, headgear (boxing, wrestling, etc.), sports gloves (baseball, boxing, hockey, lacrosse, etc), bike seats, masks (hockey, catcher, lacrosse, etc.), shoulder pads, knee pads, shin pads, elbow pads, weight belts, athletic supporters, goggles, saddles, hand grips (fitness equipment, tennis racquets, baseball bats, etc.), sports clothing including wetsuits, drysuits, padded garments (biking shorts, etc.) and conformable garments.

Conformable gels could be used in health care applications like orthopedic devices, prosthetic appliances, denture plates, hearing aids, various braces (ankle, neck, knee, etc.), conformable padding for crutches, wheelchairs, casting bandaging, splints, etc.

A variety of other consumer and industrial uses are also possible for these conformable gels. These would include women's brassieres, eyeglass and sunglass nose bridges and ear supports, seating and furniture (chairs, beds, sofas, car seats, baby seats etc.), headphones (aviation, protective, studio, consumer audio), shoulder and hand rests for telephones, keyboards, etc., conformable toys and models, teething rings, and conformable packaging for shipping.

Oil field Applications. The applications will include all those where an increase in viscosity is advantageous. The applications also include those where a controllable decrease in viscosity would also be advantageous, such as underbalanced drilling.

The polymer system would allow good gas entrainment inside the well, which would help maintain a homogeneous density and uniform pressure throughout the well. While at the surface the decrease in viscosity would allow for good separation of the gases and particulate (cuttings), allowing for a cleaner mud to be pumped back into the hole. The polymer system would have the properties of Xanthan gum while in the well without the negative property of being a food source for microbial growth and solid and gas entrainment at the surface. Also, the current fluids for underbalanced drilling are quite thin. During periods of overbalanced pressure, the fluid loss and formation damage can be quite severe because of the low viscosity of the fluid. With a thicker fluid, the invasion would be much less because the increase in viscosity would

slow down the rate of formation penetration.

Removal of cuttings. Viscosity is not a desirable trait of a drilling fluid while being pumped into the well. The viscosity is desirable in the annulus of the hole to remove cuttings from the well. The drilling fluid would be pumped into the well down the drill string. The drill string is usually cooler than the rest of the well, because it contains fluid that has recently been on the surface. The fluid would then leave the drill string and heat up. The increased viscosity would carry the cuttings to the surface. The current technology requires rigorous methods to then remove the cuttings from the fluid. The responsive polymer network based drilling fluid would cool and the carrying capacity would decrease and simple settling could be employed. The behavior would then be analogous to Xanthan gum, but in a synthetic material wherein the temperature could be modified. The responsive polymer network could also be used as a plug for cleaning out the well. Drilling would cease and the responsive polymer network-based fluid would be pumped down and the increased viscosity would clean the hole of any cuttings. Drilling with the regular fluid would then resume.

Filtration control fluid. During drilling the formation porosity could change drastically causing whole mud to enter the formation. The responsive polymer network could be pumped into the formation and as the heat from the formation warms the invading fluid, the fluid would viscosify and effectively stop the fluid from continuing to enter the formation. This could be permanent or a solution of high salinity could be pumped down to remove the viscosifying property of the responsive polymer network.

Consolidation of sand formations. During offshore drilling, the well often passes through areas of unconsolidated sands or shallow water flows. The responsive polymer network could be pumped down and viscosify with the change in temperature. The formation would then be stable enough to drill through. Cement could then be poured to further stabilize the formation. This would not need to be reversible.

Zonal shutoff tool. If during drilling, you wanted to temporarily seal a section of the well, the fluid could be pumped into place and the temperature would solidify the material. This could latter be removed by cooling the section with water or by pumping down a brine to remove the viscosifying property from the responsive polymer network.

Other commercial applications. The responsive polymer network may have additional benefits not described above. One would be the ability to provide a toy which modified shape and then set to firm that shape. Another would be as a

thermally-triggered mechanical device such as a sensor or valve. The ability of the responsive polymer network gel to hold a hydrophobic material in the presence of an aqueous solution will also be useful in the preparation of non-greasy ointments, where it is desired to reduce the amount of organic solvent. The reverse thermal gel could be useful in a gel preform, as reverse of "lost wax" castings. In this case, the gel would retain its shape as the object is formed and on cooling, it would turn to liquid and could then be drained from the preform.

The possible applications of such a reversibly gelling composition are numerous and include, by way of example only, as oil and lubricant additives, food additives, emulsion additives, use in electrophoresis and chromatography, as adhesives and binding agents, and as curing agents. They may be useful to provide initial green strength in a liquid system while it is being cured or may be used to slow delivery of an additive at high temperature. The responsive polymer network composition may be used in shoes, shoe liners, brassieres or other articles of clothing, or medical prosthetic devices to provide conformation, fit and comfort. The responsive polymer network composition may be useful in a condom as a coating which would in response to body temperature provide a degree of mechanical stiffness to the condom-responsive polymer network system. The responsive polymer network composition may be used in thermo-mechanical device, such as a sensor or valve. It may also be used as an in-situ plug which gels at higher temperature and then releases at a lower temperature. As an example, the responsive polymer network composition would be useful as a temporary block to the flow of urine. Then, for example, by lowering the temperature or by exceeding the holding strength of the plug, the flow of urine could be made to occur.

The thermally reversible gel could be useful for fire containment, such that it would viscosify when a fire started and keep burning liquid from spreading. Another example is a gel which is liquid in a fire extinguisher and becomes a gel when it comes in contact with a hot object. The gel composition of the invention may be useful as an energy absorber at high temperatures where other systems break down. The gel may be useful to open and close pores in clothing or other fabric articles in response to heat. An example is a hot mitt, which is "breathable" at room temperature and would close down when exposed to heat. The gel may be useful in supercritical fluids system. The gel retains its properties at supercritical conditions and could therefore provide a mechanism for separating something in a supercritical system. For example, the gel is a liquid at room temperature, and is raised to supercritical conditions at which point a gel

is formed. The pressure is then lowered but not to room temperature, so that the gel retains whatever it surrounded.

The responsive polymer network complexes and aqueous gels of the present invention may be understood with reference to the following examples, which are provided for the purposes of illustration and which are in not way limiting of the invention.

Example 1 This example describes the synthesis of a responsive polymer network and an aqueous responsive polymer network solution prepared using a triblock polymer of ethylene oxide and propylene oxide (Pluronic® F27) and poly(acrylic acid). This example also characterizes the gelation and the physical properties of the resultant responsive polymer network.

Synthesis. Block copolymer of propylene oxide (PO) and ethylene oxide (EO) having sandwich structure $(EO)_A(PO)_B(EO)_A$ (Pluronic F127 NF, Poloxamer 407 NF, where "F" means Flakes, "12" means $12 \times 300 = 3600$ - MW of the poly(propylene oxide) section of the block copolymer, "7" ethylene oxide in the copolymer is 70 wt%, and nominal molecular weight is 12,600) from BASF (3.0 g) was dissolved in 3.0 g acrylic acid (Aldrich). This represents a substantially 1:1 molar ratio of Pluronic® F127 and polyacrylic acid. The solution was deaerated by N_2 bubbling for 0.5 h and following addition of 100 μ l of freshly prepared saturated solution of ammonium persulfate (Kodak) in deionized water was kept at 70 °C for 16 h resulting in a transparent polymer.

Viscosity measurements. A known amount of the resultant polymer was suspended in 100 ml deionized water into which NaOH was added. Following swelling for 3 days while stirring, the pH of the resulting fine suspension was adjusted to 7. Samples of 15 ml each were taken, and pH in each vial was adjusted to desired value by addition of 1 M HCl or NaOH. Samples were then kept overnight and their viscosities were measured at different temperatures using Brookfield viscometer using either an SC4-18 or an SC4-25 spindle.

A control experiment was done with a physical blend of Pluronic® F127 and polyacrylic acid (MW 450,000) available from Aldrich. Pluronic® F127 and polyacrylic acid were dissolved together in deionized water at 1 wt% total polymer concentration and the resultant solution was adjusted to pH 7, stirred and kept in refrigerator. The responsiveness of the responsive polymer network composition and the physical blend to temperature and pH is illustrated in Figs. 1, 2 and 5. Figs. 1 and 2 clearly

demonstrate that the synthetic route outlined above resulted in a responsive polymer network polymeric system that is sensitive to pH and temperature of the environment. Note that the liquid-gel transition is very sharp, occurring over a very small temperature change or ΔpH . Fig. 5 is a viscosity vs. temperature graph comparing the gelling characteristics of the responsive polymer network composition and the physical blend. The blend prepared by physically mixing of the triblock EO/PO/EO polymer and polyacrylic acid did not exhibit viscosifying effect either as a function of temperature or pH.

It was generally observed that 1-5 wt% responsive polymer network compositions made of Pluronic® F127 and polyacrylic acid viscosify at temperatures of around 30 °C and higher if pH is adjusted to 6 or higher. The gelling effect was observed in responsive polymer network compositions standing 3 months or longer. Repeated heating and cooling of responsive polymer network compositions did not cause deterioration of the responsive polymer network or the gelling effect. Solutions of either Pluronic F127 or polyacrylic acid (1-5 w% in water, adjusted to pH 6 or higher) or physical blends of the two lacked the gelling effects found for responsive polymer network compositions.

Responsive polymer network structure. Solutions (1 wt% each) of responsive polymer network composition, a polyacrylic acid (alone) polymerized without Pluronic® and Pluronic® F127 (alone) were subjected to gel permeation chromatography analysis using triple detector system (light scattering, viscometer, and refractive index detection, Viscotek). The results of molecular weight determination are outlined in Table 1.

Table 1. Results of molecular weight determination of polyacrylic acid in responsive polymer network, polyacrylic acid itself (PAA), and Pluronic® F127.

Parameter	Definition	responsive polymer network complex	polyacrylic acid	Pluronic F127
Number-average MW	$M_n = \sum n_i M_i / \sum n_i$	212,200	782,000	12,100
Weight-average MW	$M_w = \sum n_i M_i^2 / \sum n_i M_i$	391,100	3,096,000	12,500
z-Average	$M_z = \sum n_i M_i^3 / \sum n_i M_i^2$	775,600	14,620,000	12,900
Peak average	determined by MW standards	297,000	1,140,000	-
Polydispersity	M_w / M_n	1.84	3.96	1.03
Radius of gyration	rms distance from mass center	17.51	62.14	4.34

It can be seen from Table 1 that polyacrylic acid of the responsive polymer network composition and polyacrylic acid synthesized alone are substantially different in molecular weights and polydispersity. The presence of the triblock (EO)(PO)(EO) polymer and its interaction with the developing polyacrylic acid chains had a measurable effect on the final responsive polymer network composition. Namely, polyacrylic acid synthesized in presence of the triblock (EO)(PO)(EO) polymer is of lower molecular weight and is much more monodisperse than the polyacrylic acid prepared alone. Pluronic® was very monodisperse and its molecular weight corresponded to the data provided by the supplier. Thus, the responsive polymer network compositions of the present invention are more than the sum of two individual polymers.

Further information on the structure of the responsive polymer network may be gained using the Mark-Houwink equation. Analysis using Mark-Houwink equation

$$[\eta] = K M_v^a, \quad (1)$$

where $[\eta]$ is intrinsic viscosity of (dilute) polymer solution, M_v is viscosity-average molecular weight of the polymer, K and a are specific constants, can reveal the status of the polymeric chains. The viscosity and molecular weight data obtained for PAA and responsive polymer network are expressed in terms of equation (1), in double logarithmic coordinates so that the initial slope of the curves corresponds to the parameter a , which is a measure of branching of the polymeric chains. Results on measurement of a are collected in Table 2.

Table 2. Mark-Houwink parameter a and it's interpretation.

System	a	Interpretation
Dilute polymer solution in a good solvent	≈ 0.5	Random coil
Same	≈ 1.8	Rigid rod
1 wt% polyacrylic acid	0.477 (Log K = -1.990)	Linear
1 wt% responsive polymer network composition	1.212 (Log K = -6.646)	Highly branched
1 wt% Pluronic® F127	0.529 (Log K = -2.907)	Linear

Comparison of a values suggests that polyacrylic acid prepared by itself and Pluronic® F127 are linear, whereas the responsive polymer network composition is highly branched (see differences in a and K). Because the preparation of the responsive polymer network composition uses preformed triblock polymer, it may be reasonably assumed that the grafting of the triblock polymer onto the polyacrylic acid is the source of the branching.

Branching of polyacrylic acid in the responsive polymer network composition can explain its stability (i.e. ability of responsive polymer network composition to remain thermo-responsive in dilute solutions for many months) and also may explain the phenomena of viscosification at temperatures below the cloud point. Branched polyacrylic acid molecules interpenetrate and become entangled with each other and with the triblock (EO)(PO)(EO) polymer and thereby forms a constrained, stable structure. Because of the branching nature of the responsive polymer network composition and the degree of entanglement which arises from the preparation of the interacting network, the constituent polymers experience a much stronger degree of interaction than physically mixed polymers. These structures interact even more strongly because of the tendency of responsive components, such as the triblock (EO)(PO)(EO) polymers to form aggregates in solution.

Example 2 This example describes the synthesis of a responsive polymer network and an aqueous responsive polymer network composition prepared using Pluronic® F108 and poly(acrylic acid). This example also characterizes the gelation and the physical properties of the resultant responsive polymer network composition.

Synthesis. Block copolymer of propylene oxide (PO) and ethylene oxide (EO) having sandwich structure (EO)_A(PO)_B(EO)_A (Pluronic F108 NF, Poloxamer 338 NF, where "F" means Flakes, "10" means 10X300=3000 · MW of the poly(propylene oxide) section of the block copolymer, "8" means that the weight percentage of ethylene oxide in the copolymer is 80%, and nominal molecular weight is 14,600, 3.0 g) was dissolved

in 3.0 g acrylic acid (Aldrich). The solution was prepared as described above for Example 1.

Viscosity measurements. A known amount of the resultant polymer was suspended in 100 ml deionized water into which NaOH was added. Following swelling for 3 days while stirring, the pH of the resulting fine suspension was adjusted to 7. The responsive polymer network composition was studied as described in Example 1. responsive polymer network compositions of 1 wt% Pluronic® F108 and polyacrylic acid (1:1) viscosified at temperatures of around 34 °C and higher at pH 7, as illustrated in the viscosity vs. temperature graph in Fig. 6. Repeated heating and cooling of the responsive polymer network composition did not degrade the gelling effect. The liquid to gel transition of 34 °C correlates well with the observed characteristic temperature of 33.7 °C of the endothermic peaks that are seen in the DSC endotherm (see Fig. 7). The peaks are measured to have enthalpy value of 1.504 cal/g. This also corresponds closely to a similar endotherm observed for Pluronic® F108 alone. The observed correlation supports the conclusion that it is the formation of the triblock (EO)(PO)(EO) polymer aggregates that contribute to the gelation of the responsive polymer network compositions.

Example 3 This example describes the synthesis of a responsive polymer network and an aqueous responsive polymer network composition prepared using Pluronic®F88 Prill and poly(acrylic acid). This example also characterizes the gelation and the physical properties of the resultant responsive polymer network composition.

Synthesis. Block copolymer of propylene oxide (PO) and ethylene oxide (EO) having sandwich structure $(EO)_A(PO)_B(EO)_A$ (Pluronic F88 Prill, where "F" means Flakes, "8" means 8X300=2400 - MW of the poly(propylene oxide) section of the block copolymer, "8" means 80 wt% ethylene oxide in the copolymer is 80%, and the nominal molecular weight is 11,400, 3.0 g) was dissolved in 3.0 g acrylic acid (Aldrich). The solution was prepared as described above for Example 1.

Viscosity measurements. A responsive polymer network composition was prepared and studied as described in Example 1. responsive polymer network compositions of 1 wt% Pluronic® F88 and polyacrylic acid (1:1) viscosified at temperatures of around 48 °C and higher at pH 7, as is illustrated in the viscosity vs. temperature graph of Fig. 8. Repeated heating and cooling of responsive polymer network suspensions was not observed to cause deterioration of the gelation effect. This measurement correlates well with the observed characteristic temperature of 47 °C of the

endothermic peaks that are seen in the DSC endotherm. The peaks are measured to have enthalpy value of 0.9 cal/g.

Example 4 This Example is directed toward demonstrating that covalent cross-linking of polyacrylic acid component of responsive polymer network may be used without detrimental effect to the responsive polymer network gelation.

Pluronic® F127 NF (3.0 g) and 7.5 mg of pentaerythritol triallyl ether (crosslinking agent, Aldrich, tech., 70%) were dissolved in 3.0 g acrylic acid (Aldrich). The crosslinking agent was sufficient to lightly crosslink the polyacrylic acid. The solution was deaerated by N₂ bubbling for 20 min and following addition of 50 µl of freshly prepared 300 mg/ml solution of ammonium persulfate (Kodak) in deionized water was kept at 70 °C for 2 h resulting in a strong whitish polymer. A sample of the polymer obtained (2.0 g) was suspended in 100 ml deionized water into which 0.32 g NaOH was added. Suspended responsive polymer network particles were allowed to swell for 3 days under constant stirring. The resulting fine suspension exhibited very high viscosity at T > 30 °C and low viscosity at T < 30 °C.

Example 5 This example describes the synthesis of a responsive polymer network and an aqueous responsive polymer network composition prepared using Pluronic® P104 and poly(acrylic acid). This example also characterizes the gelation and the physical properties of the resultant responsive polymer network composition.

Block copolymer of propylene oxide (PO) and ethylene oxide (EO) having sandwich structure (EO)_A(PO)_B(EO)_A (Pluronic P104, where "P" means Paste, "10" means 10X300=3000 - MW of the poly(propylene oxide) section of the block copolymer, "4" means 40 wt% ethylene oxide in the copolymer and the nominal molecular weight is 5,900, 3.0 g) was dissolved in 3.0 g acrylic acid (Aldrich). The solution was prepared as described above for Example 1. A responsive polymer network composition was prepared and studied as described in Example 1. responsive polymer network compositions of 2 wt% Pluronic® P104 and polyacrylic acid (1:1) viscosified at temperatures of around 28 °C and higher at pH 7, as is illustrated in the viscosity vs. temperature graph of Fig. 9. Repeated heating and cooling of responsive polymer network suspensions was not observed to cause deterioration of the gelation effect.

Example 6 This example describes the synthesis of a responsive polymer network and an aqueous responsive polymer network composition prepared using Pluronic® P123 and poly(acrylic acid). This example also characterizes the gelation and

the physical properties of the resultant responsive polymer network composition.

Block copolymer of propylene oxide (PO) and ethylene oxide (EO) having sandwich structure $(EO)_A(PO)_B(EO)_A$ (Pluronic P123, where "P" means Paste, "12" means 12X300=3600 - MW of the poly(propylene oxide) section of the block copolymer, "3" means 30 wt% ethylene oxide in the copolymer and the nominal molecular weight is 5,750, 3.0 g) was dissolved in 3.0 g acrylic acid (Aldrich). The solution was prepared as described above for Example 1. A responsive polymer network composition was prepared and studied as described in Example 1. responsive polymer network compositions of 2 wt% Pluronic® P104 and polyacrylic acid (1:1) viscosified at temperatures of around 25 °C and higher at pH 7, as is illustrated in the viscosity vs. temperature graph of Fig. 10. Repeated heating and cooling of responsive polymer network suspensions was not observed to cause deterioration of the gelation effect.

Example 7 The following example demonstrates the effect of hydrophilic/hydrophobic ratio on the gelling temperature. Responsive polymer network compositions were prepared from the following triblock copolymers shown in Table 3.

Table 3. Composition of triblock polymers investigated.

poloxamer composition	MW of PO block	wt% of EO block
$(EO)_{37}(PO)_{56}(EO)_{37}$	3250	50
$(EO)_{25}(PO)_{56}(EO)_{25}$	3250	40
$(EO)_{16}(PO)_{56}(EO)_{16}$	3250	30

Table 3 shows that in this series, the fraction of EO is reduced when the molecular weight of the PO block is kept constant. In a paper by Linse (*Macromol.* 26:4437-4449 (1993)), phase diagrams for these copolymers in water were calculated and it was shown that two-phase boundaries corresponding to the beginning of aggregation are almost unaffected by the molecular mass, given a constant EO/PO ratio, whereas these boundaries shifted to lower temperature as the EO content of the polymer is reduced at constant mass. The strong dependence of the EO/PO ratio is a consequence of the differing solubilities of EO and PO in water at the elevated temperatures. Thus one would suppose that aggregation that causes viscosification in the responsive polymer network composition should shift to lower temperature as EO fraction decreases.

The poloxamer (3.0 g) was dissolved in 3.0 g acrylic acid. The solution was deaerated by N₂ bubbling for 20 min. and following addition of the 100 μ l of freshly prepared saturated solution of ammonium persulfate in deionized water was kept at 70°C for 16 h resulting in a strong whitish polymer. A sample of the polymer obtained
 5 (0.4 g) was suspended in 40 ml deionized water into which NaOH was added. Suspended responsive polymer network particles were allowed to dissolve under constant stirring. The resulting 1 wt% responsive polymer network solutions were subjected to the viscosity measurement at shear rate of 132 or 13.2 sec⁻¹ using a SC4-18 spindle. It can be seen from Fig. 11 that, firstly, viscosity of the 1 wt% responsive
 10 polymer network solutions before viscosification (at 20-24°C) increases in the series (EO)₃₇(PO)₅₆(EO)₃₇ > (EO)₂₅(PO)₅₆(EO)₂₅ > (EO)₁₆(PO)₅₆(EO)₁₆ and, secondly, the temperature at which gelation shifts from about 45°C for (EO)₃₇(PO)₅₆(EO)₃₇ to about 35°C for (EO)₂₅(PO)₅₆(EO)₂₅ and (EO)₁₆(PO)₅₆(EO)₁₆. Both results are in excellent agreement with the theory set forth in Linse.

15 Example 8 This example demonstrates the ability to shift the temperature at which a polymer network gel viscosifies by addition of a salt into the aqueous solution.

The polymer network was prepared as described in Example 1. The dry polymer was placed into either deionized water or a 0.5 M NaCl solution. in proportions to provide a 2.5 wt% solution. Viscosity profiles for the two aqueous
 20 solutions were determined and are reported in Fig. 12. The viscosity of a 2.5 wt% solution in deionized water has a higher initial viscosity than that in a 0.5M NaCl solution at 20°C. Further, the temperature at which gelation occurs shifts from about 35°C in water to about 30°C in the NaCl solution. Thus, a change in the ionic strength of the aqueous gel composition alters its gelling properties.

25 Example 9 This example describes the synthesis of a responsive polymer network and an aqueous responsive polymer network composition prepared using Pluronic® F127 and poly(acrylic acid) with a 75% reduction in ammonium persulfate initiator, relative to Example 1.

Pluronic F127 NF grade from BASF (3.0g) was dissolved in 5 grams of Acrylic
 30 Acid (Aldrich). The solution took approximately 30 minutes to solubilize. The solution was deaerated for 15 minutes and 25 μ L of a 0.1gram/2mL ammonium persulfate (Kodak) in deionized water solution was added. The solution was heated in a bead bath at 70°C for 20 minutes. A white polymer is formed and is then removed from the tube, cut into small pieces, and placed in a dish to dry overnight. A 3% by weight

solution of dry polymer to deionized water is prepared to allow the polymer to solubilize. To neutralize the solution approximately 0.3g of NaOH (Fisher) is added to the solution prior to solubilizing of the polymer. The polymer pieces solubilize at neutral pH over a period of 48 - 72 hours. The viscosity of the solution increased at 37°C when tested using a Brookfield viscometer.

Example 10 This example describes the synthesis of a responsive polymer network and an aqueous responsive polymer network composition prepared using Pluronic® F127 and poly(acrylic acid) with a 50% reduction in ammonium persulfate initiator, as compared to example 1.

Pluronic F127 NF grade from BASF (3.0g) was dissolved in 5 grams of Acrylic Acid (Aldrich). The solution took approximately 30 minutes to solubilize. The solution was deaerated for 15 minutes and 50uL of a 0.1gram/2mL ammonium persulfate (Kodak) in deionized water solution was added. The solution was heated in a bead bath at 70°C for 20 minutes. A white polymer is formed and is then removed from the tube, cut into small pieces, and placed in a dish to dry overnight. A 3% by weight solution of dry polymer to deionized water is prepared to allow the polymer to solubilize. To neutralize the solution approximately 0.3g of NaOH (Fisher) is added to the solution prior to solubilizing of the polymer. The polymer pieces solubilize at neutral pH over a period of 48 - 72 hours. The viscosity of the solution increased at 37°C when tested using a Brookfield viscometer.

Example 11 This example describes the synthesis of a responsive polymer network and an aqueous responsive polymer network composition prepared using Pluronic® F127 and poly(acrylic acid) with twice the amount of ammonium persulfate initiator, as compared to Example 1.

Pluronic F127 NF grade from BASF (3.0g) was dissolved in 5 grams of Acrylic Acid (Aldrich). The solution took approximately 30 minutes to solubilize. The solution was deaerated for 15 minutes and 100uL of a 0.1gram/1mL ammonium persulfate (Kodak) in deionized water solution was added. The solution was heated in a bead bath at 70°C for 20 minutes. A white polymer is formed and is then removed from the tube, cut into small pieces, and placed in a dish to dry overnight. A 3% by weight solution of dry polymer to deionized water is prepared to allow the polymer to solubilize. To neutralize the solution approximately 0.3g of NaOH (Fisher) is added to the solution prior to solubilizing of the polymer. The polymer pieces solubilize at neutral pH over a period of 48 - 72 hours. The viscosity of the solution increased at

37°C when tested using a Brookfield viscometer.

Example 12 This example describes the synthesis of a responsive polymer network and an aqueous responsive polymer network composition prepared using Pluronic® F127 and poly(acrylic acid) with AIBN as initiator.

5 Pluronic F127 NF grade from BASF (3.0g) was dissolved in 5 grams of Acrylic Acid (Aldrich). The solution took approximately 30 minutes to solubilize. The solution was deaerated for 15 minutes and 50uL of a 0.1gram/1mL alpha,alpha'-azoisobutyronitrile (Aldrich) in acetone was added. The solution was heated in a bead bath at 70°C for 20 minutes. A white polymer is formed and is then removed from the
10 tube, cut into small pieces, and placed in a dish to dry overnight. A 3% by weight solution of dry polymer to deionized water is prepared to allow the polymer to solubilize. To neutralize the solution approximately 0.3g of NaOH (Fisher) is added to the solution prior to solubilizing of the polymer. The polymer pieces solubilize at neutral pH over a period of 48 - 72 hours. The viscosity of the solution increased at
15 40°C when tested using a Brookfield viscometer.

Example 13 This example describes the synthesis of a responsive polymer network and an aqueous responsive polymer network composition prepared using Pluronic® F127 and poly(acrylic acid) with Vazo 52 as initiator.

Pluronic F127 NF grade from BASF (3.0g) was dissolved in 5 grams of Acrylic
20 Acid (Aldrich). The solution took approximately 30 minutes to solubilize. The solution was deaerated for 15 minutes and 200uL of a 0.1gram/1mL Vazo 52 (Dupont) in acetone solution was added. The solution was heated in a bead bath at 70°C for 20 minutes. A white polymer is formed and is then removed from the tube, cut into small pieces, and placed in a dish to dry overnight. A 3% by weight solution of dry polymer
25 to deionized water is prepared to allow the polymer to solubilize. To neutralize the solution approximately 0.3g of NaOH (Fisher) is added to the solution prior to solubilizing of the polymer. The polymer pieces solubilize at neutral pH over a period of 48 - 72 hours. The viscosity of the solution increased at 37°C when tested using a Brookfield viscometer.

30 Example 14 This example describes the synthesis of a responsive polymer network and an aqueous responsive polymer network composition prepared using Pluronic® F127 and poly(acrylic acid) with 25% water added.

Pluronic F127 NF grade from BASF (2.25g) was dissolved in 3.75 grams of Acrylic Acid (Aldrich) and 2g of deionized water. The solution took approximately 30

minutes to solubilize. The solution was deaerated for 15 minutes and 50uL of a 0.1gram/1mL ammonium persulfate (Kodak) in deionized water solution was added. The solution was heated in a bead bath at 70°C for 20 minutes. A white polymer is formed and is then removed from the tube, cut into small pieces, and placed in a dish to dry overnight. A 3% by weight solution of dry polymer to deionized water is prepared to allow the polymer to solubilize. To neutralize the solution approximately 0.3g of NaOH (Fisher) is added to the solution prior to solubilizing of the polymer. The polymer pieces solubilize at neutral pH over a period of 48 - 72 hours. The viscosity of the solution increased at 35°C when tested using a Brookfield viscometer.

10 Example 15 This example describes the synthesis of a responsive polymer network and an aqueous responsive polymer network composition prepared using Pluronic® F127 and poly(acrylic acid) with 35% water added.

Pluronic F127 NF grade from BASF (1.95g) was dissolved in 3.25grams of Acrylic Acid (Aldrich) and 2.8g of deionized water. The solution took approximately 15 30 minutes to solubilize. The solution was deaerated for 15 minutes and 50uL of a 0.1gram/1mL ammonium persulfate (Kodak) in deionized water solution was added. The solution was heated in a bead bath at 70°C for 20 minutes. A white polymer is formed and is then removed from the tube, cut into small pieces, and placed in a dish to dry overnight. A 3% by weight solution of dry polymer to deionized water is prepared 20 to allow the polymer to solubilize. To neutralize the solution approximately 0.3g of NaOH (Fisher) is added to the solution prior to solubilizing of the polymer. The polymer pieces solubilize at neutral pH over a period of 48 - 72 hours. The viscosity of the solution increased at 37°C when tested using a Brookfield viscometer.

Example 16 This example describes the synthesis of a responsive polymer 25 network and an aqueous responsive polymer network composition prepared using Pluronic® F127 and poly(acrylic acid) with 25% water added and a 50% reduction in ammonium persulfate initiator, as compared to Example 1.

Pluronic F127 NF grade from BASF (2.25g) was dissolved in 3.75 grams of Acrylic Acid (Aldrich) and 2g of deionized water. The solution took approximately 30 30 minutes to solubilize. The solution was deaerated for 15 minutes and 50uL of a 0.1gram/1mL ammonium persulfate (Kodak) in deionized water solution was added. The solution was heated in a bead bath at 70°C for 20 minutes. A white polymer is formed and is then removed from the tube, cut into small pieces, and placed in a dish to dry overnight. A 3% by weight solution of dry polymer to deionized water is prepared

to allow the polymer to solubilize. To neutralize the solution approximately 0.3g of NaOH (Fisher) is added to the solution prior to solubilizing of the polymer. The polymer pieces solubilize at neutral pH over a period of 48 - 72 hours. The viscosity of the solution increased at 37°C when tested using a Brookfield viscometer.

5 Example 17 This example describes the synthesis of a responsive polymer network and an aqueous responsive polymer network composition prepared using Pluronic® F127/Pluronic® F108 blend (1:1) and poly(acrylic acid).

Pluronic F127 NF grade from BASF (1.50g) and Pluronic F108 from BASF (1.50g) was dissolved in 5 grams of Acrylic Acid (Aldrich). The solution took
10 approximately 30 minutes to solubilize. The solution was deaerated for 15 minutes and 50uL of a 0.1gram/1mL ammonium persulfate (Kodak) in deionized water solution was added. The solution was heated in a bead bath at 70°C for 20 minutes. A white polymer is formed and is then removed from the tube, cut into small pieces, and placed in a dish to dry overnight. A 3% by weight solution of dry polymer to deionized water
15 is prepared to allow the polymer to solubilize. To neutralize the solution approximately 0.3g of NaOH (Fisher) is added to the solution prior to solubilizing of the polymer. The polymer pieces solubilize at neutral pH over a period of 48 - 72 hours. The viscosity of the solution increased at 42°C when tested using a Brookfield viscometer.

20 Example 18 This example describes the synthesis of a responsive polymer network and an aqueous responsive polymer network composition prepared using Pluronic® F88 and poly(acrylic acid). This example illustrates the effect of the responsive component on the gelation temperature of the composition.

Pluronic F88 from BASF (3.0g) was dissolved in 5 grams of Acrylic Acid (Aldrich). The solution took approximately 30 minutes to solubilize. The solution was
25 deaerated for 15 minutes and 50uL of a 0.1gram/1mL ammonium persulfate (Kodak) in deionized water solution was added. The solution was heated in a bead bath at 70°C for 20 minutes. A white polymer is formed and is then removed from the tube, cut into small pieces, and placed in a dish to dry overnight. A 3% by weight solution of dry polymer to deionized water is prepared to allow the polymer to solubilize. To
30 neutralize the solution approximately 0.3g of NaOH (Fisher) is added to the solution prior to solubilizing of the polymer. The polymer pieces solubilize at neutral pH over a period of 48 - 72 hours. The viscosity of the solution increased at 80°C when tested using a Brookfield viscometer

Example 19 This example describes the synthesis of a responsive polymer

network and an aqueous responsive polymer network composition prepared using Pluronic® F127/Pluronic® F88 blend (1:1) and poly(acrylic acid). This example illustrates the effect of the responsive component on the gelation temperature of the composition.

5 Pluronic F127 NF grade from BASF (1.50g) and Pluronic F88 from BASF (1.50g) was dissolved in 5 grams of Acrylic Acid (Aldrich). The solution took approximately 30 minutes to solubilize. The solution was deaerated for 15 minutes and 50uL of a 0.1gram/1mL ammonium persulfate (Kodak) in deionized water solution was added. The solution was heated in a bead bath at 70°C for 20 minutes. A white polymer is
10 formed and is then removed from the tube, cut into small pieces, and placed in a dish to dry overnight. A 3% by weight solution of dry polymer to deionized water is prepared to allow the polymer to solubilize. To neutralize the solution approximately 0.3g of NaOH (Fisher) is added to the solution prior to solubilizing of the polymer. The polymer pieces solubilize at neutral pH over a period of 48 - 72 hours. The viscosity of
15 the solution increased at 85°C when tested using a Brookfield viscometer.

Example 20 This example describes the synthesis of a responsive polymer network and an aqueous responsive polymer network composition prepared using Pluronic® F127 and poly(acrylic acid) using suspension polymerization.

Pluronic F127 NF grade from BASF (15.0g) was dissolved in 25 grams of acrylic
20 acid (Aldrich). The solution was deaerated for 40 minutes while it solubilized and 250uL of a 0.5gram/1mL ammonium persulfate (Kodak) in deionized water solution was added. The continuous phase solvent, heptane, was added to a 500mL baffled reaction vessel equipped with an R100 impeller blade. A surfactant Ganex V216 0.5 wt% was added to the continuous phase. The continuous phase was heated to 60°C while being
25 deaerated for 75 minutes. The polymer solution is then added to the reaction vessel while stirring and allowed to react 2 hours. Then, 250 µl of APS solution is added and stirring is continued for an additional 14 h. The heptane is decanted from the white polymer beads and the polymer is washed twice with an excess of hexane to remove residual heptane on the surface of the beads. A 3% by weight solution of dry polymer
30 to deionized water is prepared to allow the polymer to solubilize. To neutralize the solution approximately 0.3g of NaOH (Fisher) is added to the solution prior to solubilizing of the polymer. The polymer pieces solubilize at neutral pH over a period of 48 - 72 hours. The viscosity of the solution increased at 37°C when tested using a Brookfield viscometer.

Example 21 This example describes the synthesis of a responsive polymer network gel composition prepared using Pluronic F127 and a copolymer of methacrylic and acrylic acid.

Methacrylic acid (Aldrich, 0.2 g) and acrylic acid (Aldrich, 1.8 g) were mixed and used to dissolve 2.0 g Pluronic® F127. The solution was deaerated for 0.5 h and, following addition of 100 µl freshly prepared saturated solution of ammonium persulfate in deionized water, was kept at 70°C for 16 h resulting in a transparent polymer. A sample of the polymer was suspended in deionized water with added NaOH. Following swelling for three day, pH was adjusted to 9.0. A 2 wt% composition viscosified at temperatures of 40°C and higher. Viscosity vs. temperature profile is shown in Fig. 13.

Example 22 This example describes the synthesis of a responsive polymer network and an aqueous responsive polymer network composition prepared using Pluronic® F127 and poly(acrylic acid) using suspension polymerization.

261.4 g of a 50 wt% sodium hydroxide (Fisher) solution in deionized water was added to 4.2 kg acrylic acid (Aldrich) kd. The solution was mixed to allow the resultant precipitate to solubilize. 3.5 kg Pluronic F127 NF grade (BASF) was added to the acrylic acid solution with agitation. The solution was deaerated for three (3) hours while it solubilized. 39.0 L of the continuous phase solvent (Norpar 12) was added to a 30 gallon stainless steel reaction vessel equipped with baffles and a heating/cooling jacket. Two (2) A-200 impeller blades were mounted on the agitator shaft to provide mixing. Ganex V-126 surfactant was added to the continuous phase at 0.3 wt% (based on total batch size). The continuous phase was deaerated for three (3) hours with agitation. 26.7g benzoyl peroxide 75% (Akzo) was dissolved in 0.5 kg acrylic acid. This initiator system was then added to the Pluronic/acrylic acid monomer solution and allowed to mix for 30 minutes. The monomer solution was transferred to the reaction vessel via a diaphragm pump. The reaction vessel agitator was set at 600 RPM, and the entire contents of the vessel were deaerated for an additional one (1) hour. The reaction vessel temperature was ramped to reaction temperature using a tempered heating water unit. The reaction was allowed to continue for 14 hours under a continuous nitrogen sparge. At the completion of the reaction, the reactor contents were discharged into clean containers. The bulk of the Norpar phase is decanted from the polymer beads. The remaining slurry is vacuum filtered to remove residual Norpar. The filtered polymer beads are then dried under vacuum for three (3) hours at 50 degrees centigrade.

Example 23 This example describes the formation of gel beads of the invention.

Pluoronic F88 from BASF (35.2) was dissolved in 42.1 grams of Acrylic Acid (Aldrich) with 1.32 NaOH in 2.5 mL deionized water. The solution took approximately 30 minutes to solubilize. The solution was deaerated for 20 minutes and a 0.53 gram/5 gram benzoyl peroxide in acrylic acid solution was added. The continuous phase, Norpar (Exxon), was added to a 500 ml baffled reaction vessel equipped with a R100 impellar blade. Ganez V216 (0.2 wt%) was added to the continuous phase. The continuous phase was then deaerated for 35 minutes. The polymer solution is then added to the reaction vessel with stirring. The vessel is heated to 70° C and allowed to react for 12 hours. The bulk of the Norpar is decanted from the white polymer beads and the polymer is vacuum filtered and washed once with heptane. Then the beads are vacuum oven dried for 3 hours at 50° C. A 1 wt% solution is prepared with approximately 300 mL of a 5N NaOH (Fisher) solution added to neutralize. This solution shows reverse thermal viscosification.

Example 24 Pluoronic F127 NF grade from BASF (140.8 g) was dissolved in 169.96 grams of acrylic acid (Aldrich) with 10.5 grams of a 50 wt% NaOH solution. The solution was deaerated for 45 minutes while it solubilized and of a 1.1 gram/25.2 gram benzoyl peroxide in acrylic acid solution was added. The continuous phase solvent, Norpar (Exxon), was added to a 2000 ml water jacketed baffled reaction vessel equipped with three A200 impellar blades. Ganez V216 (0.3 wt%) was added to the continuous phase. The continuous phase was deaerated for 60 minutes. The polymer solution is then added to the reaction vessel with stirring at a speed 650 rpm. The vessel is heated to 70° C and the reaction continues for 12 hours. The bulk of the Norpar is decanted from the white polymer beads and the polymer is vacuum filtered and rinsed once with heptane. Then the beads are vacuum oven dried for 3 hours at 50° C. A 1 wt% solution is prepared with approximately 300 mL of a 5N NaOH (Fisher) solution added to neutralize. This solution shows reverse thermal viscosification.

Example 25 This example describes the synthesis of a responsive polymer network gel composition prepared using Pluronic® F88 and poly(acrylic acid). This example demonstrates gelation of the responsive polymer network under conditions typically found in oil drillings.

A 3 wt% responsive polymer network gel was prepared from Pluronic F88 and polyacrylic acid (1:1) according to the method described in Example 1. The viscosity profile of the solution was determined at elevated pressures. Fig. 14 illustrates the solution performance at 5000 psi. The responsive polymer network experiences an

increase in viscosity at above 100°F and remains viscous under oil drilling conditions, namely temperatures in the range of 150-200°F.

Example 26 The aim of this Example is three-fold: (i) to demonstrate responsive polymer network compositions using a responsive component other than triblock polyoxyalkylene copolymers, (ii) to preserve useful properties of responsive polymer network, namely, ease of synthesis, viscosifying at body temperature, bioadhesiveness, and entirely benign components, and (iii) to incorporate drug into the responsive polymer network composition. For these purposes, nonylphenyl ether of polyethyleneglycol (Nonoxynol 9, drug name is Igepal CO-630) was chosen. This remarkable compound is surface active, possesses cloud point at around 55 °C and is used as a spermicide and anti-HIV agent in vaginal applications. Synthesis and properties of the resulted responsive polymer network are described below.

Synthesis. Igepal®CO-630 (Rhone-Poulenc) (3.0 g) was dissolved in 3.0 g acrylic acid (Aldrich). The solution was deaerated by N₂ bubbling for 30 min and following addition of 100 µl of freshly prepared 300 mg/ml solution of ammonium persulfate (Kodak) in deionized water was kept at 70 °C for 16 h resulting in a transparent solid polymer. A sample of the polymer obtained (2.0 g) was suspended in 100 ml deionized water into which 0.18 g NaOH was added. Suspended responsive polymer network particles were allowed to swell for 1 day under constant stirring. The pH of the solution was adjusted to 7.0.

Viscosity measurement. Viscosity *vs* temperature effect for responsive polymer network made of Nonoxanol 9 and polyacrylic acid (1:1) in deionized water (pH 7) is presented in Fig. 15. The viscosity is measured at shear rate of 2.64 sec⁻¹ using a SC4-18 spindle which allows a very sensitive measurement. It can be seen that the responsive polymer network starts to viscosify at about 30 °C and the viscosity approaches maximum at 55 °C at which point aggregates are formed (cloudiness is developed) and the viscosity drops precipitously.

Example 27 The following example is related to responsive polymer network performance in drug release. Drug loading and kinetics of release of the protein hemoglobin from a responsive polymer network composition are presented.

Synthesis. Pluronic F127 ® (3.0 g) was dissolved in 3.0 g acrylic acid. The solution was deaerated by N₂ bubbling for 0.5 h and following addition of 100 µl of freshly prepared saturated solution of ammonium persulfate (Kodak) in deionized water was kept at 70 °C for 16 h resulting in a transparent polymer. The resultant responsive

polymer network obtained (5 g) was suspended in 95 ml deionized water into which NaOH was added. The resulting suspension was allowed to swell for 7 days.

Hemoglobin loading and release. A 5 wt% responsive polymer network composition (3 g) was allowed to swell for 16 h in 10 ml of 0.25 mg/ml solution of human hemoglobin (Sigma) in deionized water adjusted to pH 8. The resulting mixture was well shaken and placed into the feed chambers of customized vertical, static, Franz-like diffusion cells made of Teflon. The feed and receiver chambers of the diffusion cells were separated by mesh screens (# 2063). The receiver chamber was continuously stirred by a magnetic bar. The cells were allowed to equilibrate to either 25 or 37 °C (in an oven). The feed and receiver phases consisted of 1 g of the hemoglobin-loaded responsive polymer network and 6 ml of phosphate-buffered saline (pH 7.4), respectively. In the control experiment, the feed phase was made of 1 g of 0.25 mg/ml hemoglobin solution. After the feed solution had been loaded into the cell, the kinetic time commenced. Samples of the receiver phase was withdrawn from time to time and their absorbance was measured spectrophotometrically at 400 nm. To calculate hemoglobin concentrations, corresponding calibration curves (absorbance in PBS versus hemoglobin concentration) were generated. The results of the kinetic experiment are presented in Fig. 16. It can be seen that the rate of hemoglobin release from responsive polymer network was substantially lowered at 37 °C when compared to that at 25 °C, because of viscosity increase in responsive polymer network at elevated temperatures (see Fig. 1). The protein released from the responsive polymer network composition still retained its native structure, as was determined by comparison of uv-vis spectra of release hemoglobin and natural hemoglobin.

Example 28 Drug loading and kinetics of release of the protein lysozyme from a responsive polymer network composition is reported. The responsive polymer network composition was prepared as described in Example 19.

Lysozyme loading and release. A 5 wt% responsive polymer network composition (3 g) was allowed to swell for 16 h in 10 ml of 1 mg/ml solution of chicken egg-white lysozyme (Sigma) and 1.5 mg/ml sodium dodecyl sulfate (Aldrich) in deionized water adjusted to pH 8.5. The resulting mixture was well shaken and placed into the feed chambers of customized vertical, static, Franz-like diffusion cells made of Teflon. The feed and receiver chambers of the diffusion cells were separated by mesh screens (# 2063). The receiver chamber was continuously stirred by a magnetic bar. The cells were allowed to equilibrate to either 25 or 37 °C (in an oven). The feed and

receptor phases consisted of 1 g of the lysozyme-loaded responsive polymer network and 6 ml of phosphate-buffered saline (pH 7.4), respectively. In the control experiment, the feed phase was made of 1 g of 1 mg/ml lysozyme solution. After the feed solution had been loaded into the cell, the kinetic time commenced. Samples were withdrawn and their absorbance measured spectrophotometrically at 280 nm. A calibration curve was prepared for lysozyme concentration ranging from 0 mg/ml to 0.5 mg/ml in phosphate buffered saline. The results of the kinetic experiment are presented in Fig. 17. It can be seen that the rate of lysozyme release from the responsive polymer network composition was substantially lowered at 37 °C when compared to that at 25 °C, because of viscosity increase in responsive polymer network at elevated temperatures (see Fig. 1).

In order to demonstrate the retention of the enzymatic activity of lysozyme, the lysozyme released from the responsive polymer network composition was assayed using *Micrococcus lysodeikticus* cells and compared to that of original lysozyme. The enzymatic activity of lysozyme was the same, within the error of the assay (15%), as that of the original lysozyme. Control without lysozyme in presence of sodium dodecyl sulfate did not show any appreciable lysis of the cells.

Example 29 Drug loading and kinetics of release of insulin from a responsive polymer network composition is reported. The responsive polymer network composition was prepared as described in Example 19.

Insulin loading and release. A 5 wt% responsive polymer network composition (3 g) was allowed to swell for 16 h in 10 ml of 5 mg/ml solution of bovine Zn²⁺-insulin (Sigma) in deionized water adjusted to pH 7. The resulting mixture was well shaken and placed into the feed chambers of customized vertical, static, Franz-like diffusion cells made of Teflon. The feed and receiver chambers of the diffusion cells were separated by mesh screens (# 2063). The receiver chamber was continuously stirred by a magnetic bar. The cells were allowed to equilibrate to either 25 or 37 °C (in an oven). The feed and receiver phases consisted of 1 g of the insulin-loaded responsive polymer network and 6 ml of phosphate-buffered saline (pH 7.4), respectively. In the control experiment, the feed phase was made of 1 g of 5 mg/ml insulin solution. After the feed solution had been loaded into the cell, the timing commenced. Samples were withdrawn and their absorbance was measured spectrophotometrically at 280 nm. A calibration curve was prepared for insulin concentration ranging from 0 mg/ml to 1.25 mg/ml in phosphate buffered saline. The results of the kinetic experiment are presented in Fig.

18. The rate of insulin release from responsive polymer network was substantially lowered at 37 °C when compared to that at 25 °C, because of viscosity increase in responsive polymer network at elevated temperatures (see Fig. 1).

Example 30 Drug loading and kinetics of release of insulin from a responsive polymer network composition is reported. The responsive polymer network composition was prepared as described in Example 19.

Solutions for release studies were prepared as follows. A simulated tear solution including 3.35 g NaCl, 1.00 g NaHCO₃, and 0.04g CaCl₂ · 2H₂O was prepared by dissolving the salts in 500 ml total volume deionized water. Solution A was prepared by dissolving 0.34 g Timolol in a 3% w/w solution of responsive polymer network in simulated tear solution to a total weight of 10.0 g. Solution B was prepared by dissolving 0.34 g Timolol in simulated tear solution to a total weight of 10.0 g. Solution C was prepared by dissolving 0.34 g Timolol in a 2% w/w solution of responsive polymer network lightly crosslinked with 25% crosslinker in simulated tear solution to a total weight of 10.0 g.

Release study. A 250 µL aliquot of Solutions A, B, and C were placed in shallow plastic pans with a total capacity of about 300 µL. A piece of screen (30 mesh) was placed over the top of each pan and fixed in place. The same procedure was repeated again for Solutions A and B so that samples could be run at 34 °C and ambient temperature.

A 25.0 ml sample of the tear solution was placed in each of five small beakers. Three of the beakers were left on the counter top, and two were placed in an incubator set at 34.0 °C to equilibrate for about 30 minutes. Samples of Solutions A and B intended for testing at 34 °C were placed in the same incubator so that they too would rise to the desired temperature.

The samples of Solutions A, B, and C to be tested for timolol release at room temperature were dropped into the three beakers on the counter top so that the open mesh faced down. The warmed responsive polymer network samples were also placed in their beakers in the same manner. A 150µl sample was removed from each beaker every thirty minutes for the next 2 hours and replaced with the same volume of fresh tear solution. Samples were analyzed by UV at 295 nm and compared to a standard curve to determine Timolol concentration. The results of the Timolol release study are presented in Fig. 19.

Example 31 This example demonstrates the preparation of a sterile polymer

network aqueous composition and the stability of the composition to sterilization. The polymer network is prepared as described in Example 1, except that the composition is prepared at 2 wt% Pluronic F127/polyacrylic acid. After dissolution of the 2 wt% polymer network in water, the viscosity is measured. The composition then is
5 sterilized by autoclaving at 121°C, 16 psi for 30 minutes. Viscosity is determined after sterilization. The corresponding curves for viscosity (a) before and (b) after sterilization are shown in Fig. 20 and establish that minimal change in the viscosity profile of the material has occurred with sterilization.

Example 32 This example is presented to describe the formation of a neutral
10 responsive polymer network and to describe the formation of such a network from an acrylamide monomer.

Three grams of acrylamide (99+%, Aldrich, mp 84-86°C) was thoroughly mixed with three grams of Pluronic F127 NF and 50 mg benzoin ethyl ether (99%, Aldrich, mp 59-61°C). The resulting homogeneous powder was placed into a plastic vial with a
15 rubber septum and heated to up to 90°C at which point a homogeneous liquid was obtained (by melting of the component materials). The resultant liquid was purged with nitrogen for 5 min. and then UV-illuminated with a Light-Welder 3010 EC UV spot/wand lamp (spectral output 300-500 nm, intensity 6000 mW/cm², Dymax Co, Torrington, CT) for 60 min at 90°C. A white powder was recovered and air dried
20 overnight.

A portion of the white polymer powder (1.25g) was suspended in deionized water (23.75g) to form a 5 wt% polymer solution and was allowed to hydrate for 4 days at room temperature. The resulting suspension was homogenized and then stood for another 6 days at room temperature. The resultant opaque solution was pH 6.7 and
25 displayed a viscosification vs. temperature curve as shown in Fig. 21. No hydrolysis of the acrylamide moieties was observed as characterized by Fourier Transform IR spectroscopy. While a very pronounced peak is observed at 1670 cm⁻¹ (-CO-NH₂ vibration) in both freshly made response polymer networks and in networks which were dried at 70°C, no peaks at 1720 cm⁻¹ (COOH dimers) are observed. This, along
30 with the essential neutral pH of the polymer is a good indication that the responsive polymer network is not charged.

Example 33 This example is presented to illustrate the performance changes of a polyacrylamide-based responsive polymer network with time.

Five grams of acrylamide was thoroughly mixed with five grams Pluronic F127

NF and 100 mg benzoin ethyl ether. The resulting homogeneous powder was placed into a plastic vial, sealed with a rubber septum, heated up to 100°C and simultaneously UV-illuminated by a spot/wand lamp for 60 minutes with a spectral output of 300-500 and an intensity of 6000 mW/cm². The resulting homogeneous white powder was air
5 dried for 2 hours and ground; and a portion thereof (1.25 g) was dissolved in deionized water (23.75 g) to prepare a 5 wt% polymer solution. After one day, the solution turned opaque at room temperature. Its viscosity vs. temperature performance was determined after one day (Fig. 22(a)) and again after six days (Fig. 22(b)). Note that curve 100 denotes cooling and curve 102 denotes heating performance of the polymer
10 network after one day. The curves differ significantly.

Example 34 This example is presented to demonstrate an acrylamide-based responsive polymer gel prepared with differing proportions of responsive and structural polymer components and to show performance under physiological conditions.

Ten grams of acrylamide was thoroughly mixed with five grams Pluronic F127
15 NF and 100 mg of benzoin ethyl ether. The resulting homogeneous powder was placed into a plastic vial, sealed with a rubber septum, heated up to 100°C and UV-illuminated for 60 min with a spot/wand having a spectral output of 300-500 nm and an intensity of 600 mW/cm². The resulting homogeneous white powder was air dried for 2 hours and ground; and a portion (10 g) of the white powder was dissolved in a buffer solution
20 (23.75 g) comprising 7M urea (Aldrich, 99+%), 100 mM tris(hydroxymethyl)aminomethane (Fisher, A.S.C. alkalimetric standard) and 120 mM boric acid (CVS) to result in a 20 wt% suspension. The suspension was stored for 12 days at room temperature. The viscosity vs. temperature curve is found in Fig. 23.

Medicinal and Cosmetic Formulations. Because of the surfactant nature of the
25 responsive component of the responsive polymer network composition coupled with the gelation effect of the responsive polymer network composition, it is possible to prepare a formulation which is 100% water-based, but which is lubricous and thick.

Formulations including nonionic, anionic and cationic surfactants. (a) a nonionic surfactant formulation: An O/W (oil-in-water) emulsion was made by
30 combining the following ingredients utilizing conventional mixing techniques:

Ingredient	% w/w
10 % wt. 1:1 responsive polymer network as prepared in Example 1	20.0
Emulsifying Wax NF ¹	2.5
Mineral Oil	5.0

¹ Polowax available from Croda

Into a vessel equipped with a high efficiency homogenizer, the formula amount of all ingredients is added and allowed to mix to homogeneity. This formulation contains a nonionic surfactant and gives an emulsion that is fluid at room temperature but viscifies above 32°C.

(b) a cationic surfactant formulation: An O/W (oil-in-water) emulsion was made by combining the following ingredients utilizing conventional mixing techniques:

Ingredient	% w/w
10 % wt. 1:1 responsive polymer network as prepared in Example 1	20.0
Behentrimonium Methosulfate (and) Cetearyl alcohol ¹	2.5
Mineral Oil	5.0

¹ Incroquat Behenyl TMS available from Croda

Into a vessel equipped with a high efficiency homogenizer, the formula amount of all ingredients is added and allowed to mix to homogeneity. This formulation contains a cationic surfactant and gives an emulsion that is fluid at room temperature but viscifies above 32°C.

(c) an anionic surfactant formulation: An O/W (oil-in-water) emulsion was made by combining the following ingredients utilizing conventional mixing techniques:

Ingredient	% w/w
10 % wt. 1:1 responsive polymer network as prepared in Example 1	20.0
Cetearyl Phosphate (and) Cetearyl alcohol ¹	2.5
Mineral Oil	5.0

¹ Crodatos CES available from Croda

Into a vessel equipped with a high efficiency homogenizer, the formula amount of all ingredients is added and allowed to mix to homogeneity. This formulation contains an anionic surfactant and gives an emulsion that is fluid at room temperature but viscifies above 32°C.

Vaginal Moisturizer: An oil-free, lubricous, vaginal moisturizer is made by combining the following ingredients utilizing conventional mixing techniques:

Ingredient	% w/w
10 % wt. 1:1 responsive polymer network as prepared in Example 1	20.0
Glycerin USP	5.0
PPG-2 Myristyl Ether Propionate ¹	3.0
DL-Panthenol	0.5
Germaben [®] II ²	0.1
Disodium EDTA	0.2
Citric Acid	0.01
USP Purified Water	71.19

¹ Crodamol PMP available from Croda

² Germaben[®] II available from Sutton Laboratories

To one vessel, equipped with a Lightnin' Mixer with a 3 blade paddle prop, the full amount of USP Purified Water is added. The water is then heated to 80°C and held for 20 minutes. The water is then cooled to 50°C, while maintaining the temperature, with moderate to vigorous mixing, the formula amount of Disodium EDTA, Citric Acid, DL-Panthenol, Glycerin, PPG-2 Myristyl Ether Propionate, and Germaben[®] II is added. These materials are allowed to dissolve at 50°C. After dissolution, the vessel is then cooled to 20°C. To another vessel, equipped with a high efficiency homogenizer, the formula amount of responsive polymer network is added. The responsive polymer network vessel is then cooled to 4°C. After cooling, while vigorously homogenizing, the contents of the first vessel is added to the second vessel, and allowed to mix to homogeneity.

The composition displays a flowable creamy lotion appearance with excellent moisturizing, emolliency, spreadability and absorption characteristics at room temperature, and after heating the formulation to 32°C, the composition thickens to a gel-like consistency.

Formulation for Management of Bacterial Vaginosis: An oil-free, lubricous, bacterial vaginosis treatment is made by combining the following ingredients utilizing conventional mixing techniques:

Ingredient	% w/w
10 % wt. 1:1 responsive polymer network prepared as in Example 1	20.0
Glycerin USP	5.0
Metronidazole	0.75
DL-Panthenol	0.5
Germaben [®] II ¹	0.1
Disodium EDTA	0.2
Citric Acid	0.01
USP Purified Water	75.44

¹ Germaben[®] II available from Sutton Laboratories

To one vessel, equipped with a Lightnin' Mixer with a 3 blade paddle prop, the full

amount of USP Purified Water is added. The water is then heated to 80°C and held for 20 minutes. The water is then cooled to 50°C, while maintaining the temperature, with moderate to vigorous mixing, the formula amount of Disodium EDTA, Citric Acid, DL-Panthenol, Glycerin, Metronidazole, and Germaben® II is added. These materials are allowed to dissolve at 50°C. After dissolution, the vessel is then cooled to 20°C. To another vessel, equipped with a high efficiency homogenizer, the formula amount of responsive polymer network is added. The responsive polymer network vessel is then cooled to 4°C. After cooling, while vigorously homogenizing, the contents of the first vessel is added to the second vessel, and allowed to mix to homogeneity.

The composition displays a flowable jelly appearance with excellent spreadability and absorption characteristics at room temperature, and after heating the formulation to 32°C, the composition thickens to a gel-like consistency.

Formulation for Management of Bacterial Candidiasis: An oil-free, lubricous, bacterial candidiasis treatment is made by combining the following ingredients utilizing conventional mixing techniques:

Ingredient	% w/w
10 % wt. 1:1 responsive polymer network prepared as in Example 1	20.0
Glycerin USP	5.0
Miconazole Nitrate	2.0
DL-Panthenol	0.5
Germaben® II ¹	0.1
Disodium EDTA	0.2
Citric Acid	0.01
USP Purified Water	72.19

¹ Germaben® II available from Sutton Laboratories

To one vessel, equipped with a Lightnin' Mixer with a 3 blade paddle prop, the full amount of USP Purified Water is added. The water is then heated to 80°C and held for 20 minutes. The water is then cooled to 50°C, while maintaining the temperature, with moderate to vigorous mixing, the formula amount of Disodium EDTA, Citric Acid, DL-Panthenol, Glycerin, Miconazole Nitrate, and Germaben® II is added. These materials are allowed to dissolve at 50°C. After dissolution, the vessel is then cooled to 20°C. To another vessel, equipped with a high efficiency homogenizer, the formula amount of responsive polymer network is added. The responsive polymer network vessel is then cooled to 4°C. After cooling, while vigorously homogenizing, the contents of the first vessel is added to the second vessel, and allowed to mix to homogeneity.

The composition displays a flowable jelly appearance with excellent spreadability and absorption characteristics at room temperature, and after heating the formulation to 32°C, the

composition thickens to a gel-like consistency.

Acne Medication: An oil-free, clear, anti-acne treatment is made by combining the following ingredients utilizing conventional mixing techniques:

5		Ingredient	% w/w
		10 % wt. 1:1 responsive polymer network prepared as in Example 1	20.0
		Glycerin USP	5.0
		Salicylic Acid	2.0
10		DL-Panthenol	0.5
		Germaben® II ¹	0.1
		Disodium EDTA	0.2
		USP Purified Water	72.2

¹Germaben® II available from Sutton Laboratories

15

To one vessel, equipped with a Lightnin' Mixer with a 3 blade paddle prop, the full amount of USP Purified Water is added. The water is then heated to 80°C and held for 20 minutes. The water is then cooled to 50°C, while maintaining the temperature, with moderate to vigorous mixing, the formula amount of Disodium EDTA, Citric Acid, DL-Panthenol, Glycerin, Salicylic Acid, and Germaben® II is added. These materials are allowed to dissolve at 50°C. After dissolution, the vessel is then cooled to 20°C. To another vessel, equipped with a high efficiency homogenizer, the formula amount of responsive polymer network is added. The responsive polymer network vessel is then cooled to 4°C. After cooling, while vigorously homogenizing, the contents of the first vessel is added to the second vessel, and allowed to mix to homogeneity.

25

The composition displays a flowable clear jelly appearance with excellent spreadability and absorption characteristics at room temperature, and after heating the formulation to 32°C, the composition thickens to a gel-like consistency.

Topical Hormone Delivery Formulation: An oil-free, spreadable, topical hormone treatment using estradiol as the hormone is made by combining the following ingredients utilizing conventional mixing techniques:

30

Ingredient	% w/w
10 % wt. 1:1 responsive polymer network prepared as in Example 1	20.0
Glycerin USP	5.0
Estradiol	0.1
DL-Panthenol	0.5
Germaben® II ¹	0.1
Disodium EDTA	0.2
USP Purified Water	74.1

¹ Germaben® II available from Sutton Laboratories

To one vessel, equipped with a Lightnin' Mixer with a 3 blade paddle prop, the full amount of USP Purified Water is added. The water is then heated to 80°C and held for 20 minutes. The water is then cooled to 50°C, while maintaining the temperature, with moderate to vigorous mixing, the formula amount of Disodium EDTA, DL-Panthenol, Glycerin, Estradiol and Germaben® II is added. These materials are allowed to dissolve at 50°C. After dissolution, the vessel is then cooled to 20°C. To another vessel, equipped with a high efficiency homogenizer, the formula amount of responsive polymer network is added. The responsive polymer network vessel is then cooled to 4°C. After cooling, while vigorously homogenizing, the contents of the first vessel is added to the second vessel, and allowed to mix to homogeneity.

The composition displays a flowable jelly appearance with excellent spreadability and absorption characteristics at room temperature, and after heating the formulation to 32°C, the composition thickens to a gel-like consistency.

Topical Anti-Inflammatory Delivery Formulation with Penetration Enhancer: An oil-free, spreadable, topical anti-inflammatory treatment using indomethacin as the anti-inflammatory and Azone as the penetration enhancer is made by combining the following ingredients utilizing conventional mixing techniques:

Ingredient	% w/w
10 % wt. 1:1 responsive polymer network as prepared in Example 1	20.0
Glycerin USP	5.0
Indomethacin	0.5
DL-Panthenol	0.5
Germaben® II ¹	0.1
Disodium EDTA	0.2
USP Purified Water	73.7

¹ Germaben® II available from Sutton Laboratories

To one vessel, equipped with a Lightnin' Mixer with a 3 blade paddle prop, the full amount of USP Purified Water is added. The water is then heated to 80°C and held for 20 minutes. The water is then cooled to 50°C, while maintaining the temperature, with moderate

to vigorous mixing, the formula amount of Disodium EDTA, DL-Panthenol, Glycerin, Indomethacin and Germaben® II is added. These materials are allowed to dissolve at 50°C. After dissolution, the vessel is then cooled to 20°C. To another vessel, equipped with a high efficiency homogenizer, the formula amount of responsive polymer network is added. The responsive polymer network vessel is then cooled to 4°C. After cooling, while vigorously homogenizing, the contents of the first vessel is added to the second vessel, and allowed to mix to homogeneity.

The composition displays a flowable jelly appearance with excellent spreadability and absorption characteristics at room temperature, and after heating the formulation to 32°C, the composition thickens to a gel-like consistency.

Topical Anti-Inflammatory Delivery Formulation: An oil-free, spreadable, topical anti-inflammatory treatment using hydrocortisone as the anti-inflammatory is made by combining the following ingredients utilizing conventional mixing techniques:

Ingredient	% w/w
10 % wt. 1:1 responsive polymer network as prepared in Example 1	20.0
Glycerin USP	5.0
Hydrocortisone	0.5
DL-Panthenol	0.5
Germaben® II ¹	0.1
Disodium EDTA	0.2
USP Purified Water	73.7

¹ Germaben® II available from Sutton Laboratories

To one vessel, equipped with a Lightnin' Mixer with a 3 blade paddle prop, the full amount of USP Purified Water is added. The water is then heated to 80°C and held for 20 minutes. The water is then cooled to 50°C, while maintaining the temperature, with moderate to vigorous mixing, the formula amount of Disodium EDTA, DL-Panthenol, Glycerin, Hydrocortisone and Germaben® II is added. These materials are allowed to dissolve at 50°C. After dissolution, the vessel is then cooled to 20°C. To another vessel, equipped with a high efficiency homogenizer, the formula amount of responsive polymer network is added. The responsive polymer network vessel is then cooled to 4°C. After cooling, while vigorously homogenizing, the contents of the first vessel is added to the second vessel, and allowed to mix to homogeneity.

The composition displays a flowable jelly appearance with excellent spreadability and absorption characteristics at room temperature, and after heating the formulation to 32°C, the composition thickens to a gel-like consistency.

Topical Analgesic Delivery Formulation with Penetration Enhancer: An oil-free, spreadable, topical analgesic treatment using Ibuprofen as the anti-inflammatory and Azone as the penetration enhancer is made by combining the following ingredients utilizing conventional

mixing techniques:

5

10

Ingredient	% w/w
10 % wt. 1:1 responsive polymer network as prepared in Example 1	20.0
Glycerin USP	5.0
Ibuprofen	0.5
DL-Panthenol	0.5
Germaben® II ¹	0.1
Disodium EDTA	0.2
Azone	5.0
USP Purified Water	68.7

¹ Germaben® II available from Sutton Laboratories

15

20

To one vessel, equipped with a Lightnin' Mixer with a 3 blade paddle prop, the full amount of USP Purified Water is added. The water is then heated to 80°C and held for 20 minutes. The water is then cooled to 50°C, while maintaining the temperature, with moderate to vigorous mixing, the formula amount of Disodium EDTA, DL-Panthenol, Glycerin, Azone, Ibuprofen and Germaben® II is added. These materials are allowed to dissolve at 50°C. After dissolution, the vessel is then cooled to 20°C. To another vessel, equipped with a high efficiency homogenizer, the formula amount of responsive polymer network is added. The responsive polymer network vessel is then cooled to 4°C. After cooling, while vigorously homogenizing, the contents of the first vessel is added to the second vessel, and allowed to mix to homogeneity.

25

The composition displays a flowable jelly appearance with excellent spreadability and absorption characteristics at room temperature, and after heating the formulation to 32°C, the composition thickens to a gel-like consistency.

30

Topical Hair Loss Treatment with Penetration Enhancer: An oil-free, spreadable, topical hair loss treatment using Minoxidil as the hair growth stimulant and Azone as the penetration enhancer is made by combining the following ingredients utilizing conventional mixing techniques:

35

40

Ingredient	% w/w
10 % wt. 1:1 responsive polymer network as prepared in Example 1	20.0
Glycerin USP	5.0
Minoxidil	1.0
DL-Panthenol	0.5
Germaben® II ¹	0.1
Disodium EDTA	0.2
Azone	5.0
USP Purified Water	68.2

¹ Germaben® II available from Sutton Laboratories

To one vessel, equipped with a Lightnin' Mixer with a 3 blade paddle prop, the full amount of USP Purified Water is added. The water is then heated to 80°C and held for 20 minutes. The water is then cooled to 50°C, while maintaining the temperature, with moderate to vigorous mixing, the formula amount of Disodium EDTA, DL-Panthenol, Glycerin, Azone, Minoxidil and Germaben® II is added. These materials are allowed to dissolve at 50°C. After dissolution, the vessel is then cooled to 20°C. To another vessel, equipped with a high efficiency homogenizer, the formula amount of responsive polymer network is added. The responsive polymer network vessel is then cooled to 4°C. After cooling, while vigorously homogenizing, the contents of the first vessel is added to the second vessel, and allowed to mix to homogeneity.

The composition displays a flowable jelly appearance with excellent spreadability and absorption characteristics at room temperature, and after heating the formulation to 32°C, the composition thickens to a gel-like consistency.

Topical Local Anesthetic Delivery Formulation: An oil-free, spreadable, topical local anesthetic treatment using lidocaine as the anti-inflammatory is made by combining the following ingredients utilizing conventional mixing techniques:

Ingredient	% w/w
10 % wt. 1:1 responsive polymer network (F127/AA)	20.0
Glycerin USP	5.0
Lidocaine Hydrochloride	225.0
DL-Panthenol	0.5
Germaben® II	0.1
Disodium EDTA	0.2
USP Purified Water	73.2

¹ Germaben® II available from Sutton Laboratories

To one vessel, equipped with a Lightnin' Mixer with a 3 blade paddle prop, the full amount of USP Purified Water is added. The water is then heated to 80°C and held for 20 minutes. The water is then cooled to 50°C, while maintaining the temperature, with moderate to vigorous mixing, the formula amount of Disodium EDTA, DL-Panthenol, Glycerin, Lidocaine Hydrochloride and Germaben® II is added. These materials are allowed to dissolve at 50°C. After dissolution, the vessel is then cooled to 20°C. To another vessel, equipped with a high efficiency homogenizer, the formula amount of responsive polymer network is added. The responsive polymer network vessel is then cooled to 4°C. After cooling, while vigorously homogenizing, the contents of the first vessel is added to the second vessel, and allowed to mix to homogeneity.

The composition displays a flowable jelly appearance with excellent spreadability and absorption characteristics at room temperature, and after heating the formulation to 32°C, the composition thickens to a gel-like consistency.

Insomnia Treatment with Penetration Enhancer: An oil-free, spreadable, topical hair

loss treatment using Melatonin as the sleep stimulant and Azone as the penetration enhancer is made by combining the following ingredients utilizing conventional mixing techniques:

	Ingredient	% w/w
5	10 % wt. 1:1 responsive polymer network as prepared in Example 1	20.0
	Glycerin USP	5.0
	Melatonin	1.0
	DL-Panthenol	0.5
10	Germaben® II ¹	0.1
	Disodium EDTA	0.2
	Azone	5.0
	USP Purified Water	68.2

¹ Germaben® II available from Sutton Laboratories

15

To one vessel, equipped with a Lightnin' Mixer with a 3 blade paddle prop, the full amount of USP Purified Water is added. The water is then heated to 80°C and held for 20 minutes. The water is then cooled to 50°C, while maintaining the temperature, with moderate to vigorous mixing, the formula amount of Disodium EDTA, DL-
 20 Panthenol, Glycerin, Azone, Melatonin and Germaben® II is added. These materials are allowed to dissolve at 50°C. After dissolution, the vessel is then cooled to 20°C. To another vessel, equipped with a high efficiency homogenizer, the formula amount of responsive polymer network is added. The responsive polymer network vessel is then cooled to 4°C. After cooling, while vigorously homogenizing, the contents of the first
 25 vessel is added to the second vessel, and allowed to mix to homogeneity.

The composition displays a flowable jelly appearance with excellent spreadability and absorption characteristics at room temperature, and after heating the formulation to 32°C, the composition thickens to a gel-like consistency.

Formulation for Management of Decubitis Ulcers:

30

A gel wound dressing for decubitis ulcer treatment containing a proteolytic enzyme and antiseptic is made by combining the following ingredients utilizing conventional mixing techniques:

	Ingredients	% w/w
	10% wt 1:1 responsive polymer network as prepared in Example 1	20.0
	Glycerin USP	5.0
5	Sutilains	82000 USP Units/gram
	Neomycin	0.75
	DL-Panthenol	0.5
	Germaben® II ¹	0.1
	Disodium EDTA	0.2
10	Citric Acid	0.01
	USP Purified Water	qs

¹ Germaben® II available from Sutton Laboratories

To one vessel, equipped with a Lightnin' Mixer with a 3 blade paddle prop, the full amount of USP Purified Water is added. The water is then heated to 80° C and held for 20 minutes. The water is then cooled to 50° C, while maintaining the temperature, with moderate to vigorous mixing, the formula amount of Disodium EDTA, Citric Acid, DL-Panthenol, Glycerin, Neomycin, and Germaben® II is added. These materials are allowed to dissolve at 50° C. After dissolution, the vessel is then cooled to 20° C, and the Sutilains is added. To another vessel, equipped with a high efficiency homogenizer, the formula amount of IPN is added. The IPN vessel is then cooled to 4° C. After cooling, while vigorously homogenizing, the contents of the first vessel is added to the second vessel, and allowed to mix homogeneity.

The composition displays a flowable jelly appearance with excellent spreadability and absorption characteristics at room temperature, and after heating the formulation to 32° C, the composition thickens to a gel-like consistency.

Oil-free Moisturizer: An oil-free, lubricous moisturizer is made by combining the following ingredients utilizing conventional mixing techniques:

	Ingredient	% w/w
	10% wt 1:1 responsive polymer network as prepared in Example 1	20.0
	Glycerin USP	5.0
5	PPG-2 Myristyl Ether Propionate ¹	3.0
	DL-Panthenol	0.5
	Germaben [®] II ²	0.1
	Disodium EDTA	0.2
	Citric Acid	0.01
10	USP Purified Water	71.19

¹ Crodamol PMP available from Croda

² Germaben[®] II available from Sutton Laboratories

The above ingredients are added and processed as described above for the vaginal
15 moisture. The composition displays a flowable creamy lotion appearance with excellent
emolliency, spreadability and absorption characteristics at room temperature. After
heating the formulation to 26°C, the composition thickens to a gel-like consistency.
The viscosity vs. temperature curve is shown in Fig. 24 and demonstrates that addition
of adjuvants to the composition significantly enhances the responsive polymer network
20 maximum viscosity (> 900,000 cps). The use of the responsive polymer network in the
formulation also imparts a unique viscosification effect after application to the skin,
which is not evident in typical commercial O/W emulsion formulations (See, Fig. 24).

25

1. A reversibly gelling or viscosifying polymer system, comprising:
a solvated composition comprising an associating component capable of
aggregation in response to an increase in temperature; and
a solvophilic component linked to the associating component.
- 5 2. A reversibly gelling or viscosifying polymer system, comprising:
a solvated composition, comprising:
 - (a) about 0.01 to 20 wt% of a associating component capable of aggregation
in response to an increase in temperature; and
 - 10 (b) about 0.01 to 20 wt% of a solvophilic component linked with the
associating component;wherein said composition exhibits at least a five-fold increase in viscosity upon
gelation.
- 15 3. The polymer system of claim 1, wherein the associating and solvophilic
components are linked through a direct covalent bond
4. The polymer system of claim 1, wherein the associating and solvophilic
components are linked through a linking agent.
- 20 5. The polymer system of claim 1, wherein the reversible gelation or
viscosification is characterized in that the viscosity of the system increases markedly as
temperature is increased.
- 25 6. The polymer system of claim 1, characterized in that the composition
does not exhibit a macroscopic phase separation at gelation temperature.
7. The polymer system of claim 1, wherein the system is obtained by
polymerizing the solvophilic component from a mixture of monomers capable of
30 forming the solvophilic component in the presence of the associating component.
8. The polymer system of claim 1, wherein the composition comprises a
graft copolymer.

9. The polymer system of claim 8, wherein the graft is random.
10. The polymer system of claim 1, wherein the solvent is selected from the group consisting of water, salt solutions and water with water-miscible organic compound(s).
- 5 11. The polymer system of claim 1, wherein the associating component comprises at least a hydrophobic sub-component and a hydrophilic sub-component.
- 10 12. The polymer system of claim 1, wherein the solvophilic component comprises a pH responsive polymer or oligomer.
- 15 13. The polymer system of claim 1, wherein the relative proportion of hydrophobic and hydrophilic sub-components in the associating component is selected to provide the aggregation at a gelation temperature without macroscopic phase separation.
- 20 14. The polymer system of claim 1, wherein the associating component comprises about 1 to 10 wt% solids and the solvophilic component comprises about 99 to 90 wt% solids.
- 25 15. The polymer system of claim 1, wherein the associating component is present in a range of about 11 to 20 wt% and the solvophilic component is present in a range of about 89 to 80 wt%.
- 30 16. The polymer system of claim 1, wherein the associating component comprises about 21 to 30 wt% solids and the solvophilic component comprises about 79 to 80 wt% solids.
17. The polymer system of claim 1, wherein the associating component comprises about 31 to 40 wt% solids and the solvophilic component comprises about 69 to 70 wt% solids.
18. The polymer system of claim 1, wherein the associating component comprises about 41 to 50 wt% solids and the solvophilic component comprises about 59

to 50 wt% solids.

19. The polymer system of claim 1, wherein the associating component comprises about 51 to 60 wt% solids and the solvophilic component comprises about 49 to 40 wt% solids.

20. The polymer system of claim 1, wherein the associating component comprises about 61 to 70 wt% solids and the solvophilic component comprises about 39 to 30 wt% solids.

21. The polymer system of claim 1, wherein the associating component comprises about 71 to 80 wt% solids and the solvophilic component comprises about 29 to 20 wt% solids.

22. The polymer system of claim 1, wherein the associating component comprises about 81 to 90 wt% solids and the solvophilic component comprises about 19 to 10 wt% solids.

23. The polymer system of claim 1, wherein the associating component comprises about 91 to 99 wt% solids and the solvophilic component comprises about 9 to 1wt% solids.

24. The polymer system of claim 1, wherein the solvophilic component is branched.

25. The polymer system of claim 1, wherein the solvophilic component is prepared from monomer(s) selected from the group consisting of carboxylic acids, acrylic acid, substituted acrylic acid, methacrylic acid, substituted methacrylic acids, vinylcarboxylic acids, vinylsulfonic acids, substituted vinylsulfonic acids, vinylpyrrolidone, vinylacetic acid, substituted vinylacetic acid, amines, acrylamides, substituted acrylamides, acrylate esters, substituted acrylate esters, methacrylate esters, substituted methacrylate esters, AMPS, MAPTEC, vinyl pyridine, urethanes, amino acids, thiopenes, nucleotides and ionized forms thereof.

26. The polymer system of claim 1, wherein the solvophilic component comprises polyacrylic acid or neutralized polyacrylic acid.

27. The polymer system of claim 1, wherein the solvophilic component
5 comprises a copolymer.

28. The polymer system of claim 1, wherein the structure component comprises a copolymer of acrylic acid and methacrylic acid.

10 29. The polymer system of claim 29, wherein the branching structural component has a degree of branching of greater than $\alpha = 1.0$, as determined by a Mark-Houwink plot.

15 30. The polymer system of claim 1, wherein the associating component comprises a poloxamer.

20 31. The polymer system of claim 31, wherein the poloxamer comprises a block copolymer of different oxyalkylene groups, such that at least one polymer block possesses hydrophilic characteristics and at least one block possesses hydrophobic characteristics.

32. The polymer system of claim 28, wherein the block copolymer comprise polyoxyethylene (POE) and polyoxypropylene (POP).

25 33. The polymer system of claim 31, wherein the poloxamer comprises a triblock polymer of polyoxyethylene (POE) and polyoxypropylene (POP) having the formula $(POP)_a(POE)_b(POP)_c$, where a and c are in the range of 10-50 and b is in the range of 50-70.

30 34. The polymer system of claim 1, wherein the associating component comprises a nonionic surfactant.

35. The polymer system of claim 1, wherein the associating component comprises a poly(alkyl-co-oxyalkylene) having the formula $R-(OCH_2CH_2)_n-OH$, where

R is an alkyl group.

36. The polymer system of claim 1, wherein the associating component is selected from the group consisting of cellulotics, cellulose ethers and guar gums.

5

37. The polymer system of claim 6, wherein the composition possesses a critical micelle temperature at about the temperature of gelation of the system.

38. The polymer system of claim 1, wherein the composition exhibits at least about a 10-fold increase in viscosity upon gelation over a temperature of less than 10°C.

39. The polymer system of claim 1, wherein the composition exhibits at least about a 30-fold increase in viscosity upon gelation over a temperature of less than 10°C.

15

40. The polymer system of claim 1, wherein the network is additionally responsive to environmental stimulus selected from the group consisting of temperature, pH, ionic strength, light irradiation, electric field strength and solvent composition.

20

41. A polymer composition, comprising:
an associating component capable of aggregation in response to an increase in temperature; and
a solvophilic component linked to the associating component.

25

42. Method of making a polymer network useful in preparation of a reversibly gelling polymer system, comprising:

combining an associating component, said associating component capable of aggregation in response to an increase in temperature, with a monomer capable of polymerizing into a solvophilic component; and

30

initiating polymerization of the monomer to form the solvophilic component and to link the solvophilic component to the associating component.

43. Method of making a polymer network useful in the preparation of a

reversibly gelling polymer system, comprising:

combining a solvophilic component with a monomer capable of polymerizing into an associating component, said associating component capable of aggregation in response to an increase in temperature; and

5 initiating polymerization of the monomer to form the associating component and to link the solvophilic component to the associating component.

44. Method of making a polymer system capable of gelation upon increase in temperature:

10 combining an associating component capable of aggregation in response to an increase in temperature with a monomer capable of polymerizing into a solvophilic component; and

initiating polymerization of the monomer to form a solvophilic component and to link the associating and solvophilic components, so as to form a polymer network;

15 and

solvating the polymer network.

45. The method of claim 42, 43 or 44, wherein the polymerization is carried out in neat monomer.

20

46. A composition of matter prepared according to claims 42, 43 or 44, comprising a associating component and a solvophilic component which upon hydration and/or neutralization form a polymer system.

25

47. The method of claim 42, 43 or 44, wherein a polymerization initiator is selected to provide a polymer system having a selected temperature of viscosification.

48. The method of claim 42, 43 or 44, further comprising addition of water to the solution.

30

49. The method of claim 42, 43 or 44, wherein one or more associating components are added.

50. The method of claim 42, 43 or 44, wherein one or more monomers of

the solvophilic component are added.

51. Method of making polymer network capable of reversible gelation upon exposure to an environmental stimulus, comprising:

- 5 dissolving a associating component capable of aggregation in response to a change in an environmental stimulus in a monomer of a solvophilic component;
dispersing the associating component and monomer into an insoluble organic phase with agitation to form droplets;
initiating polymerization of the monomer to form the solvophilic component, so
10 as to form a polymer network; and
collecting the polymer network as beads.

52. A method of using a reversibly gelling polymer network, comprising:
subjecting a solvated composition to a change in temperature, said solvated
15 composition comprising:

an associating component capable of aggregation in response to an increase in temperature, and a solvophilic component linked to the associating component,
wherein said solvated composition exhibits at least a five-fold increase in viscosity upon temperature change.

20

53. A drug delivery system , comprising:

an solvated composition comprising:

- (a) about 0.01 to 20 wt% of a associating component capable of aggregation
in response to an increase in temperature; and
25 (b) about 0.01 to 20 wt% of a solvophilic component linked with the associating component, wherein said solvated composition exhibits at least a five-fold increase in viscosity upon gelation; and
a pharmaceutically active component.

30

54. A system for coating a mucosal region of a mammal, comprising:

an solvated composition comprising:

- (a) about 0.01 to 20 wt% of a associating component capable of aggregation
in response to an increase in temperature; and
(b) about 0.01 to 20 wt% of a solvophilic component linked with the

associating component, wherein said solvated composition exhibits at least a five-fold increase in viscosity upon gelation;

55. A composition for topical application, comprising:
5 an solvated composition comprising:
(a) about 0.01 to 20 wt% of a associating component capable of aggregation in response to an increase in temperature; and
(b) about 0.01 to 20 wt% of a solvophilic component linked with the associating component, wherein said solvated composition exhibits at least a five-fold
10 increase in viscosity upon gelation.

56. The composition of claim 55, wherein said composition is formulated as a product selected from the group consisting of a shampoo, a sun care product, a skin care product and cosmetic.
15

57. The composition of claim 55, further comprising an additive selected from the group consisting of preservatives, humectants, emollients, surfactants, astringents, sunscreens, emulsifiers, solvents, liquefiers, colors, flavors and fragrances.

- 20 58. The composition of claim 55, wherein the gelation occurs at a temperature in the range of about 30 to 35°C.

59. The composition of claim 55, wherein the gelation occurs at a temperature in the range of about 35 to 40°C.
25

60. An emulsion which maintains viscosity over a wide range of temperatures, comprising:
an solvated composition comprising:
(a) about 0.01 to 20 wt% of a associating component capable of aggregation
30 in response to an increase in temperature; and
(b) about 0.01 to 20 wt% of a solvophilic component linked with the associating component, wherein said solvated composition exhibits at least a five-fold increase in viscosity upon gelation.

61. A thickening agent, comprising:
an solvated composition comprising:
(a) about 0.01 to 20 wt% of a associating component capable of aggregation
in response to an increase in temperature; and
5 (b) about 0.01 to 20 wt% of a solvophilic component linked with the
associating component, wherein said solvated composition exhibits at least a five-fold
increase in viscosity upon gelation.
62. An electrophoretic system, comprising:
10 an solvated composition comprising:
(a) about 0.01 to 20 wt% of a associating component capable of aggregation
in response to an increase in temperature; and
(b) about 0.01 to 20 wt% of a solvophilic component linked with the
associating component, wherein said solvated composition exhibits at least a five-fold
15 increase in viscosity upon gelation.
63. A setting agent, comprising:
an solvated composition comprising:
(a) about 0.01 to 20 wt% of a associating component capable of aggregation
20 in response to an increase in temperature; and
(b) about 0.01 to 20 wt% of a solvophilic component linked with the
associating component, wherein said solvated composition exhibits at least a five-fold
increase in viscosity upon gelation.
- 25 64. A binding agent, comprising:
an solvated composition comprising:
(a) about 0.01 to 20 wt% of a associating component capable of aggregation
in response to an increase in temperature; and
(b) about 0.01 to 20 wt% of a solvophilic component linked with the
30 associating component, wherein said solvated composition exhibits at least a five-fold
increase in viscosity upon gelation.
65. A conformational system, comprising:
an solvated composition comprising:

(a) about 0.01 to 20 wt% of a associating component capable of aggregation in response to an increase in temperature; and

(b) about 0.01 to 20 wt% of a solvophilic component linked with the associating component, wherein said solvated composition exhibits at least a five-fold increase in viscosity upon gelation

66. An oil well drilling fluid comprising:
an solvated composition comprising:

(a) about 0.01 to 20 wt% of a associating component capable of aggregation in response to an increase in temperature; and

(b) about 0.01 to 20 wt% of a solvophilic component linked with the associating component, wherein said solvated composition exhibits at least a five-fold increase in viscosity upon gelation.

67. A sensor, indicator or valve, comprising:
an solvated composition comprising:

(a) about 0.01 to 20 wt% of a associating component capable of aggregation in response to an increase in temperature; and

(b) about 0.01 to 20 wt% of a solvophilic component linked with the associating component, wherein said solvated composition exhibits at least a five-fold increase in viscosity upon gelation.

68. An adhesive comprising:
an solvated composition comprising:

(a) about 0.01 to 20 wt% of a associating component capable of aggregation in response to an increase in temperature; and

(b) about 0.01 to 20 wt% of a solvophilic component linked with the associating component, wherein said solvated composition exhibits at least a five-fold increase in viscosity upon gelation.

69. A condom comprising:
an solvated composition comprising:

(a) about 0.01 to 20 wt% of a associating component capable of aggregation in response to an increase in temperature; and

(b) about 0.01 to 20 wt% of a solvophilic component linked with the associating component, wherein said solvated composition exhibits at least a five-fold increase in viscosity upon gelation.

5 70. A teat dip comprising:

an solvated composition comprising:

(a) about 0.01 to 20 wt% of a associating component capable of aggregation in response to an increase in temperature; and

10 (b) about 0.01 to 20 wt% of a solvophilic component linked with the associating component, wherein said solvated composition exhibits at least a five-fold increase in viscosity upon gelation.

71. A prosthetic device comprising:

an solvated composition comprising:

15 (a) about 0.01 to 20 wt% of a associating component capable of aggregation in response to an increase in temperature; and

(b) about 0.01 to 20 wt% of a solvophilic component linked with the associating component, wherein said solvated composition exhibits at least a five-fold increase in viscosity upon gelation.

20

72. A paint, comprising:

an solvated composition comprising:

(a) about 0.01 to 20 wt% of a associating component capable of aggregation in response to an increase in temperature; and

25 (b) about 0.01 to 20 wt% of a solvophilic component linked with the associating component, wherein said solvated composition exhibits at least a five-fold increase in viscosity upon gelation.

73. A coating, comprising:

30 an solvated composition comprising:

(a) about 0.01 to 20 wt% of a associating component capable of aggregation in response to an increase in temperature; and

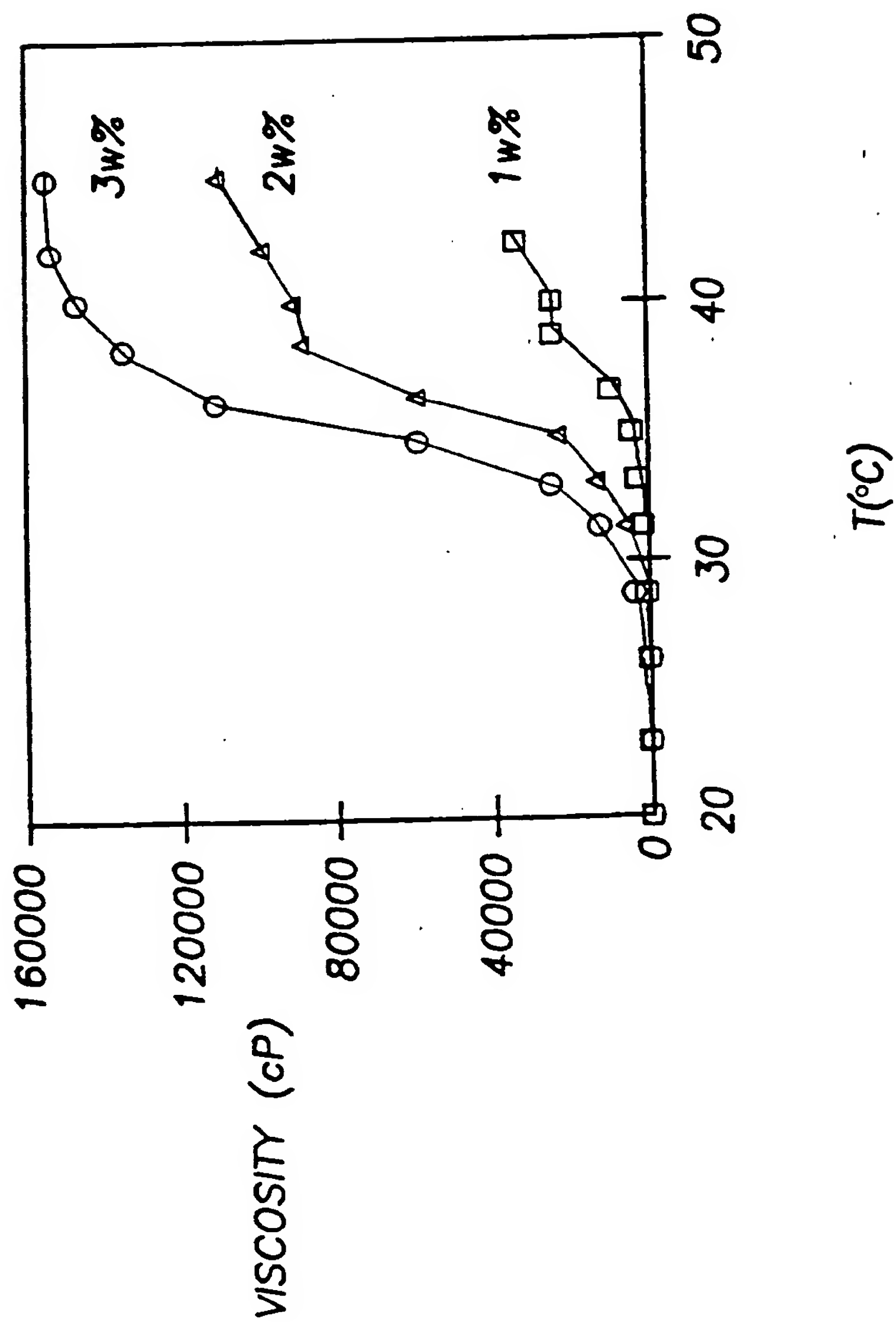
(b) about 0.01 to 20 wt% of a solvophilic component linked with the associating component, wherein said solvated composition exhibits at least a five-fold

increase in viscosity upon gelation.

74. The responsive polymer network of claim 1, characterized in that the gel remains transparent to light before and after a change in temperature.

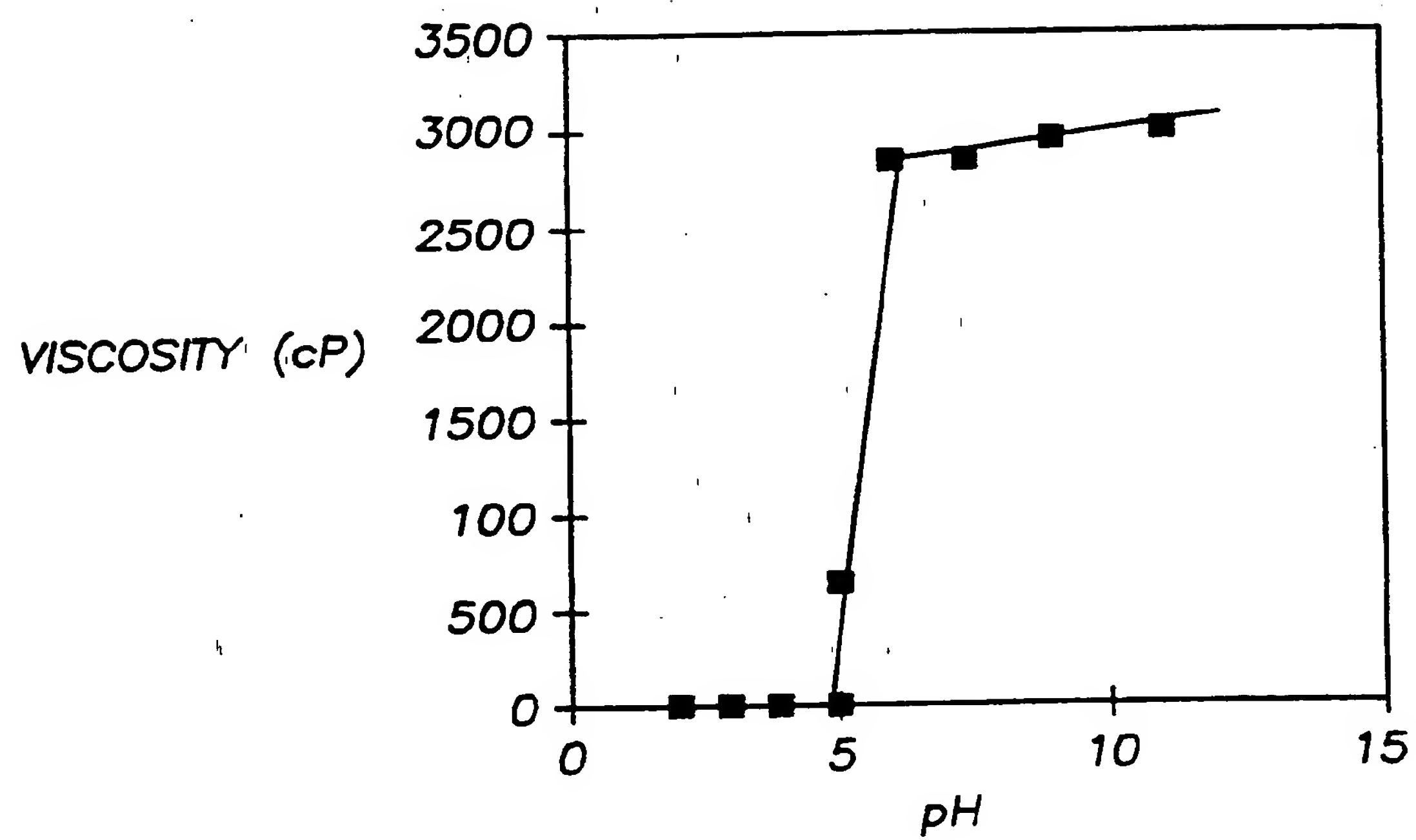
1/26

FIG. 1



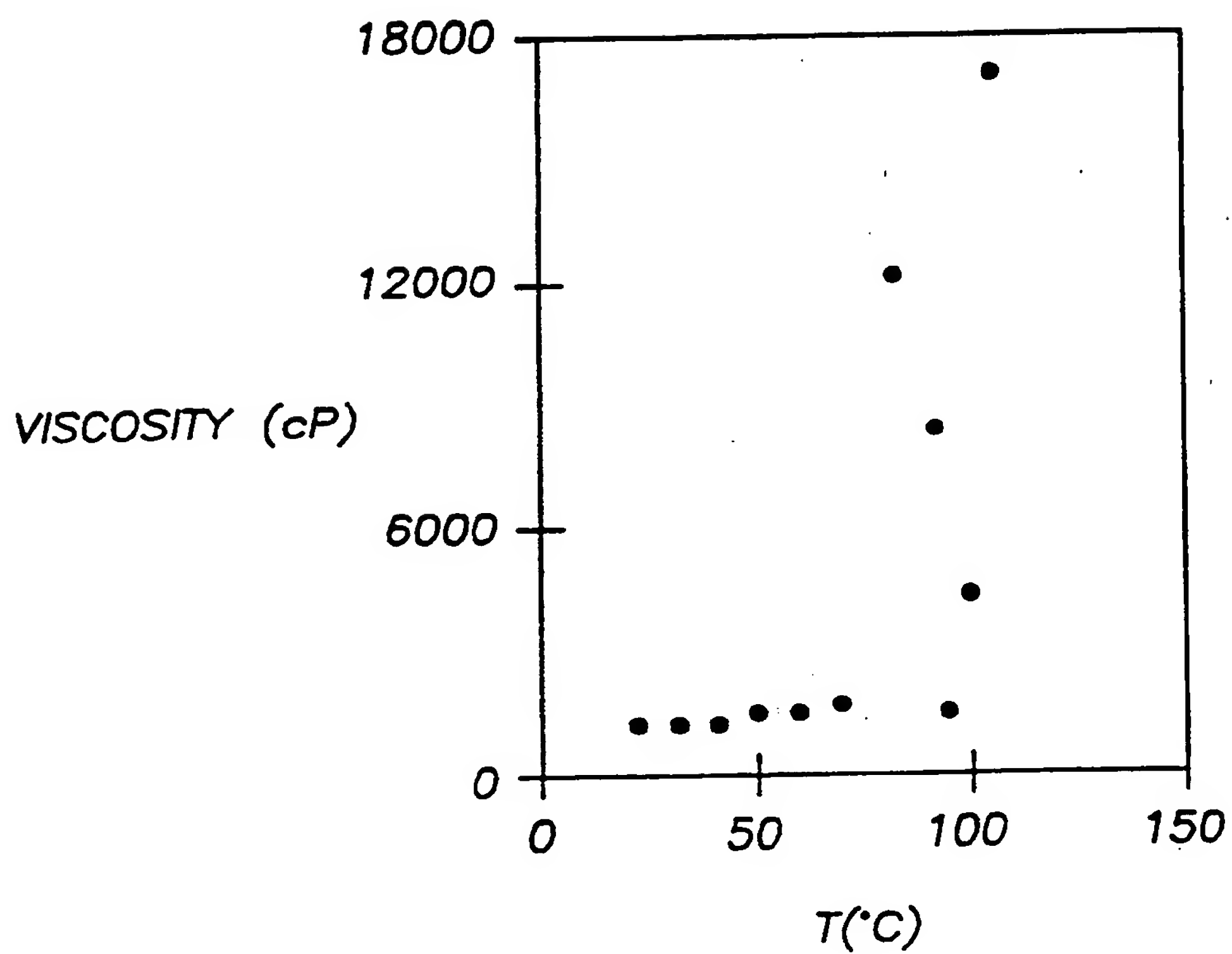
2/26

FIG:2



3/26

FIG. 3



4/26

FIG. 4a

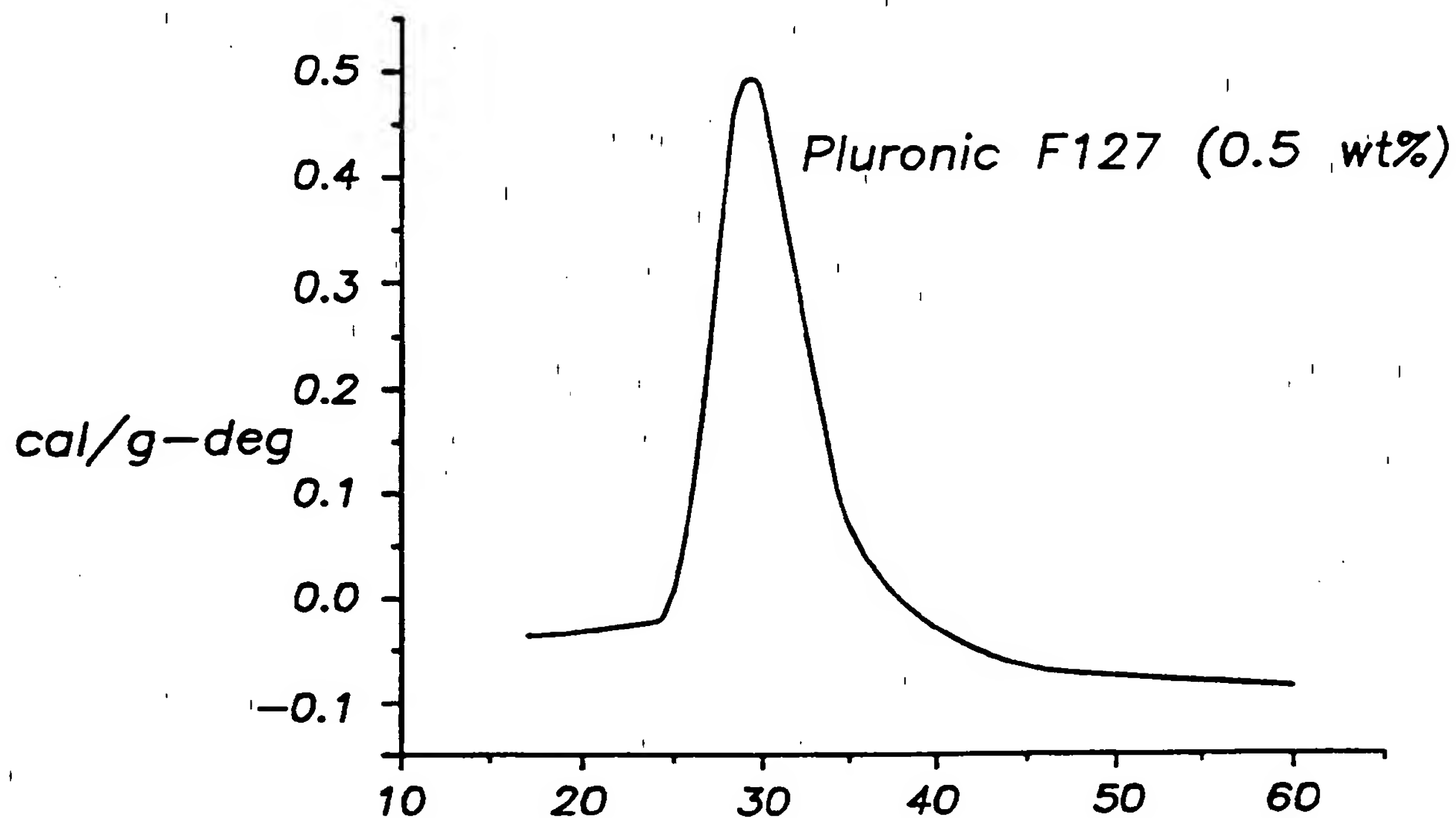
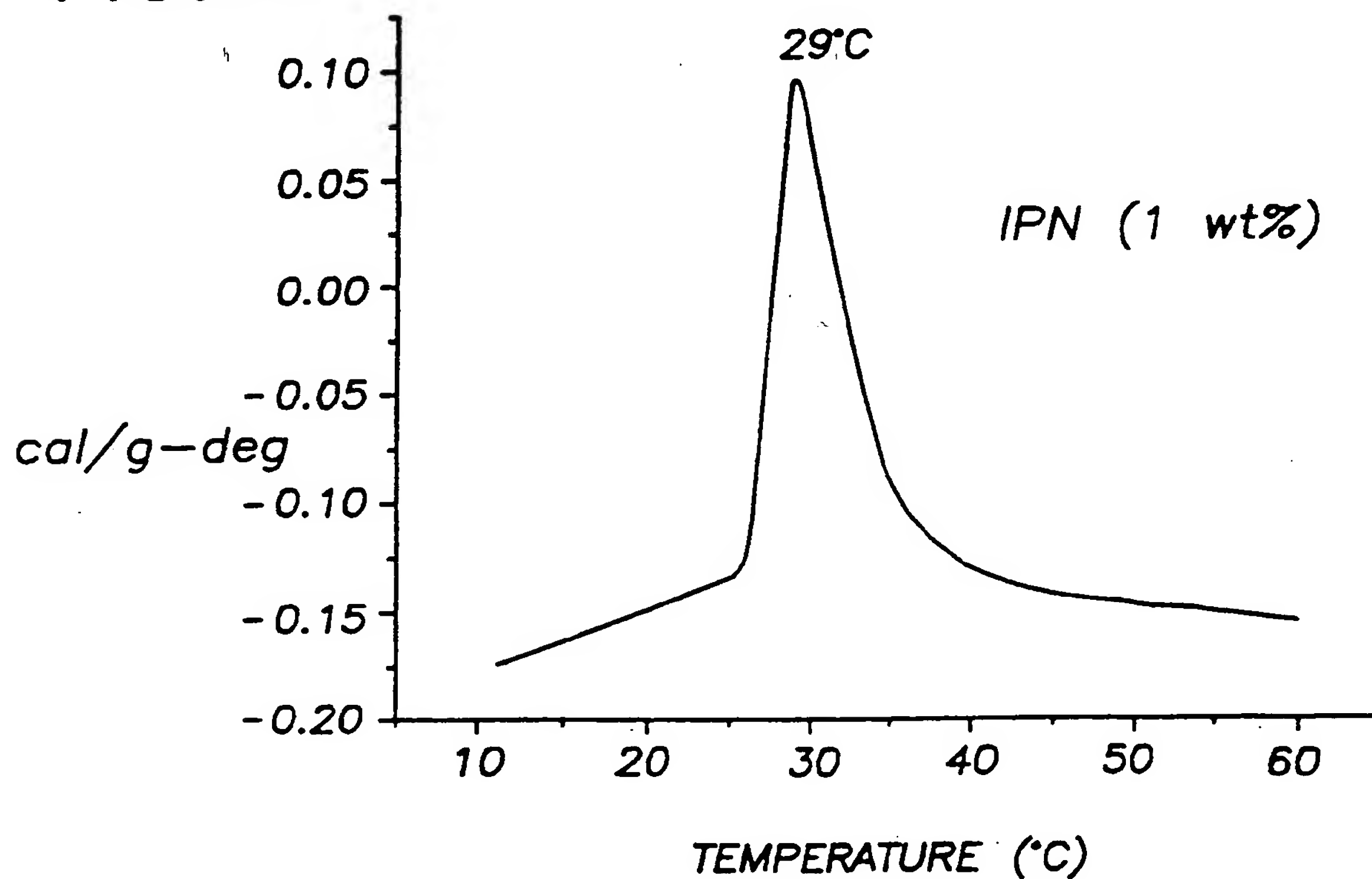
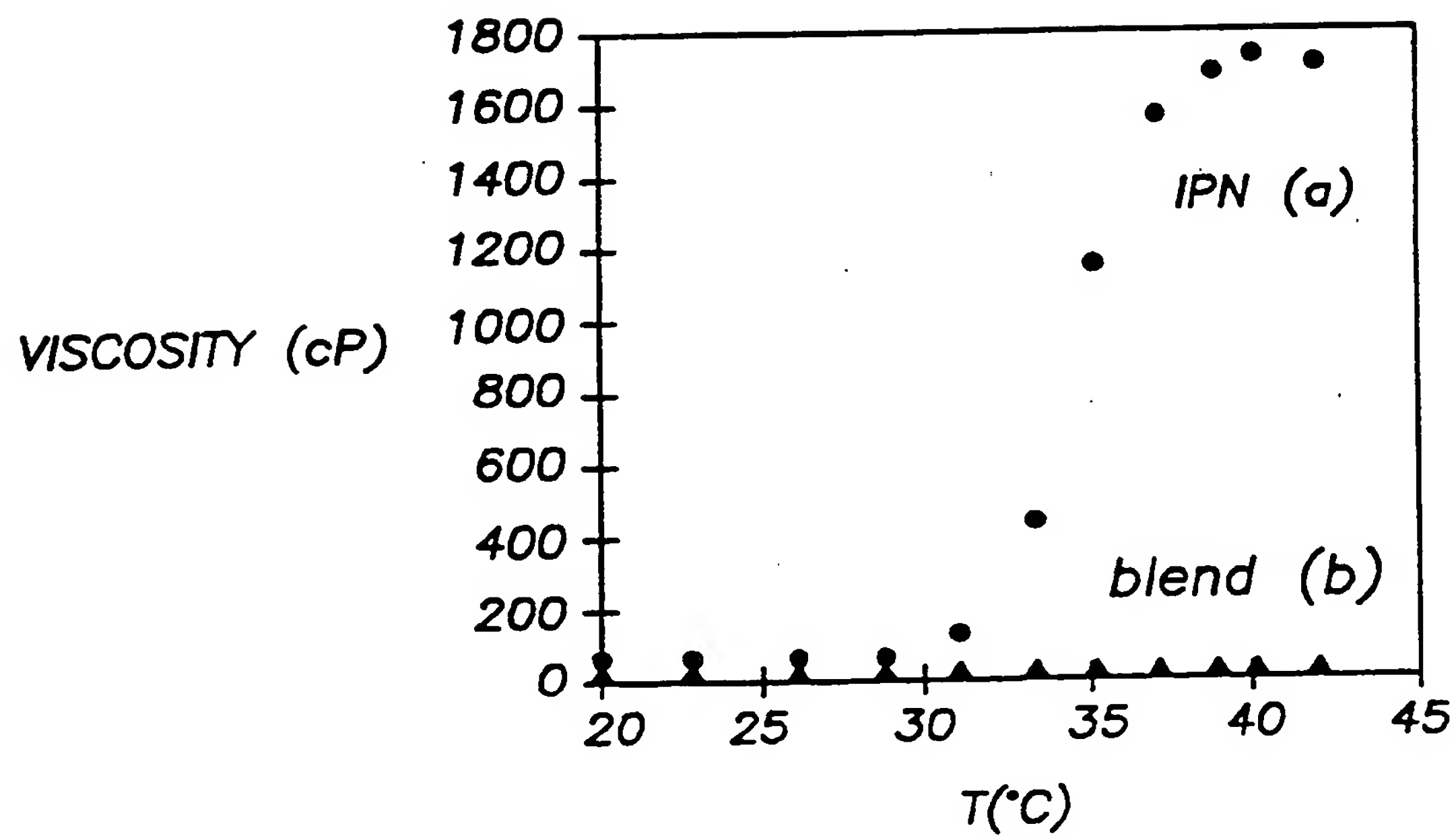


FIG. 4b



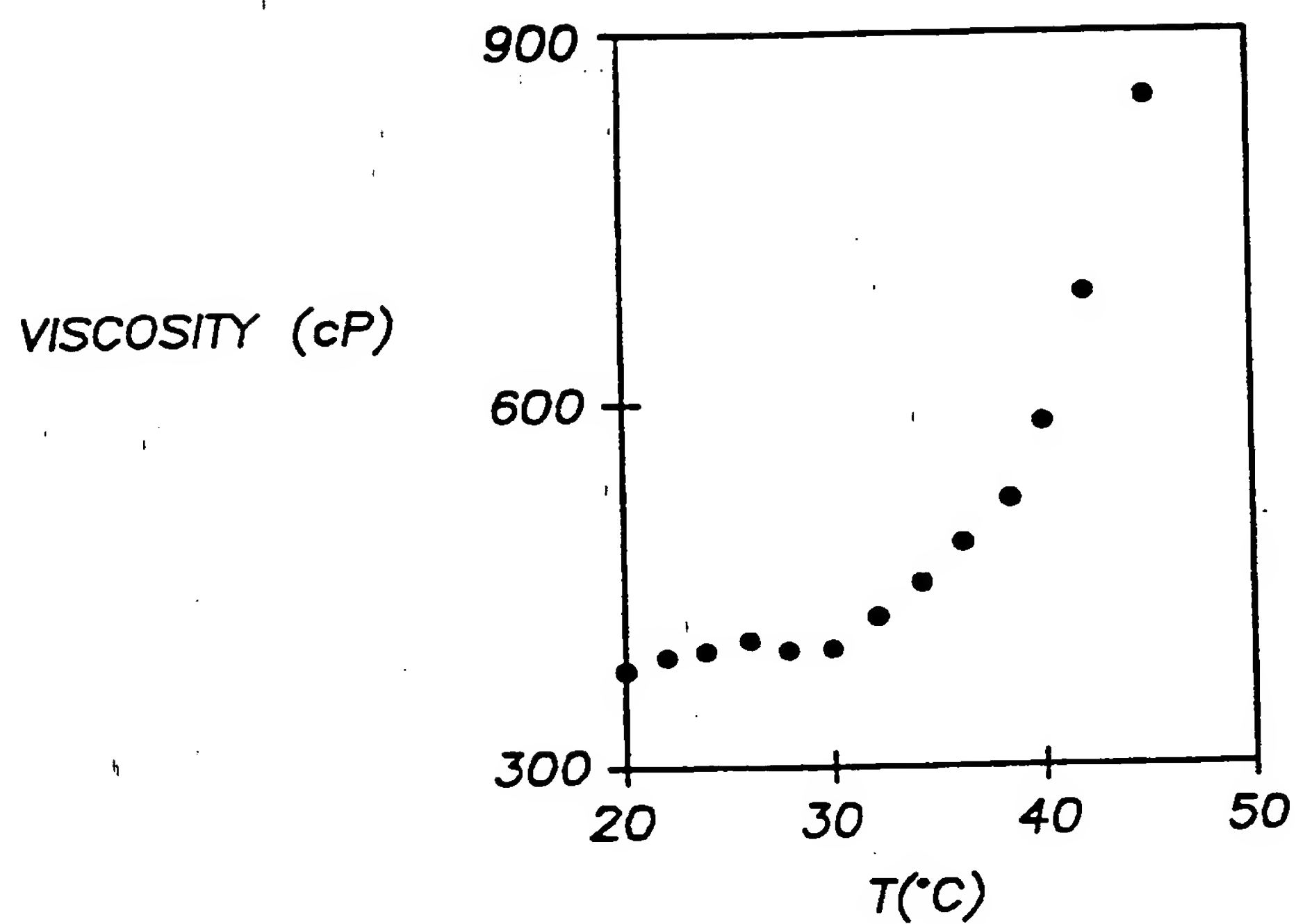
5/26

FIG. 5

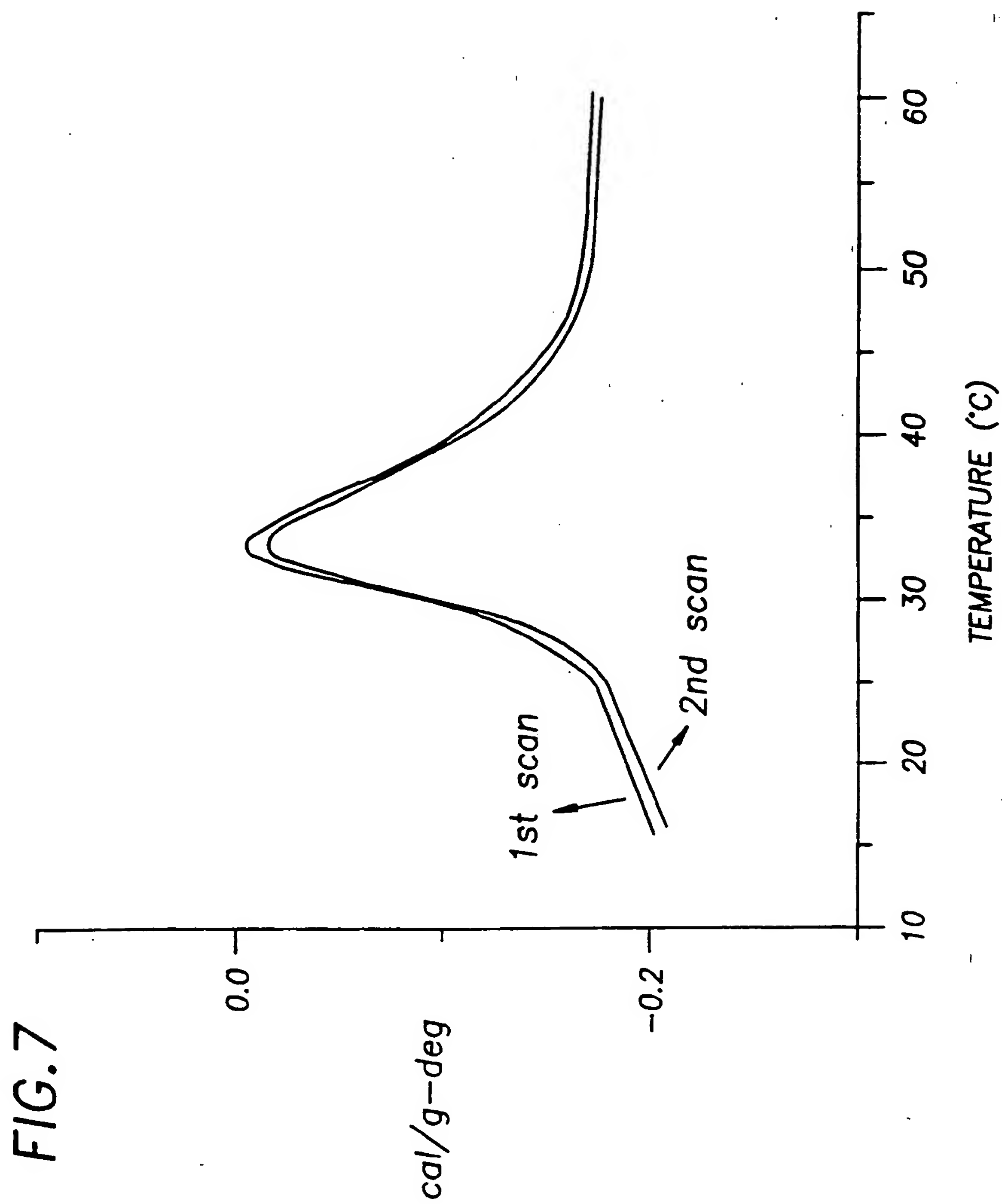


6/26

FIG. 6

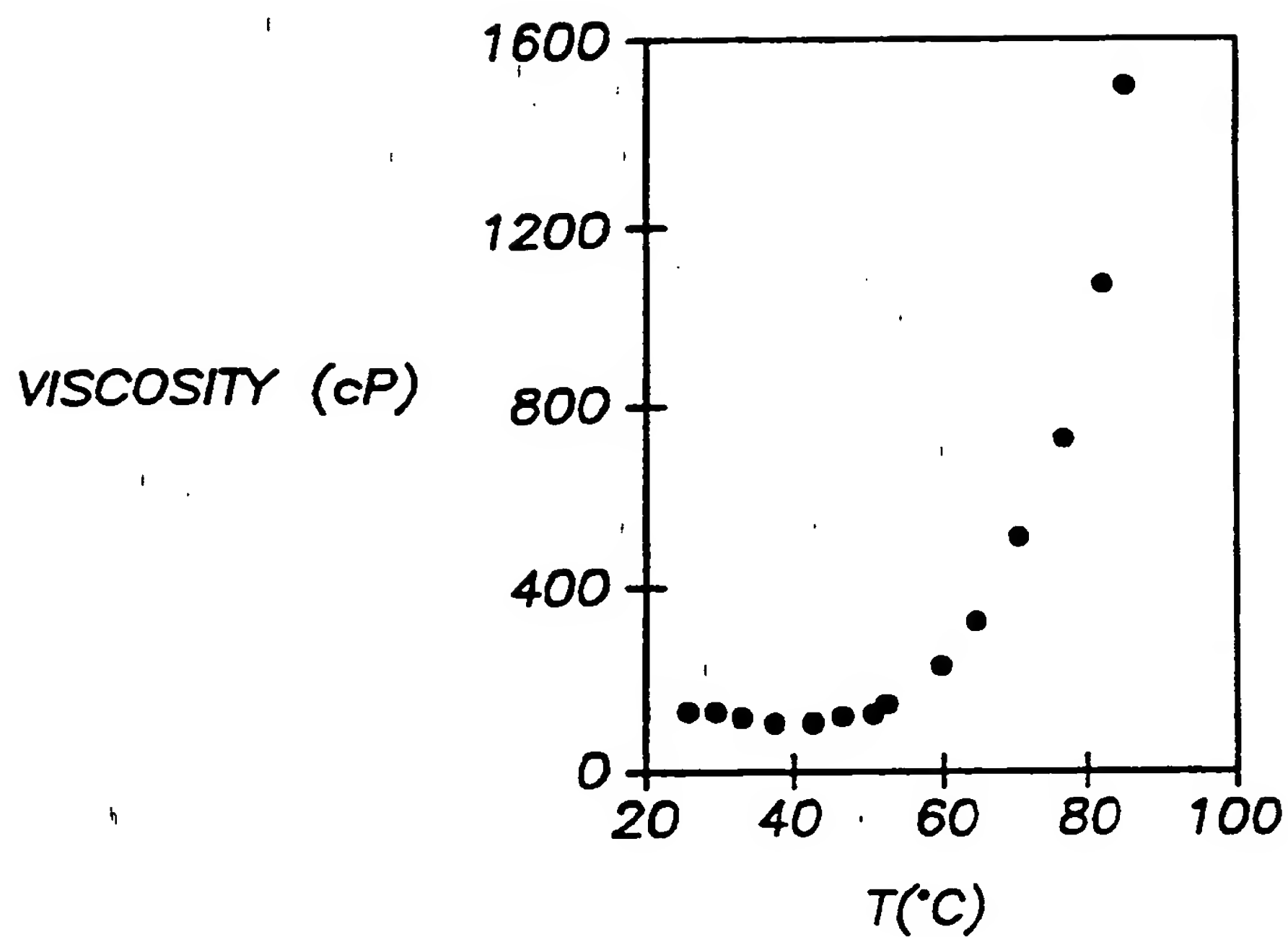


7/26



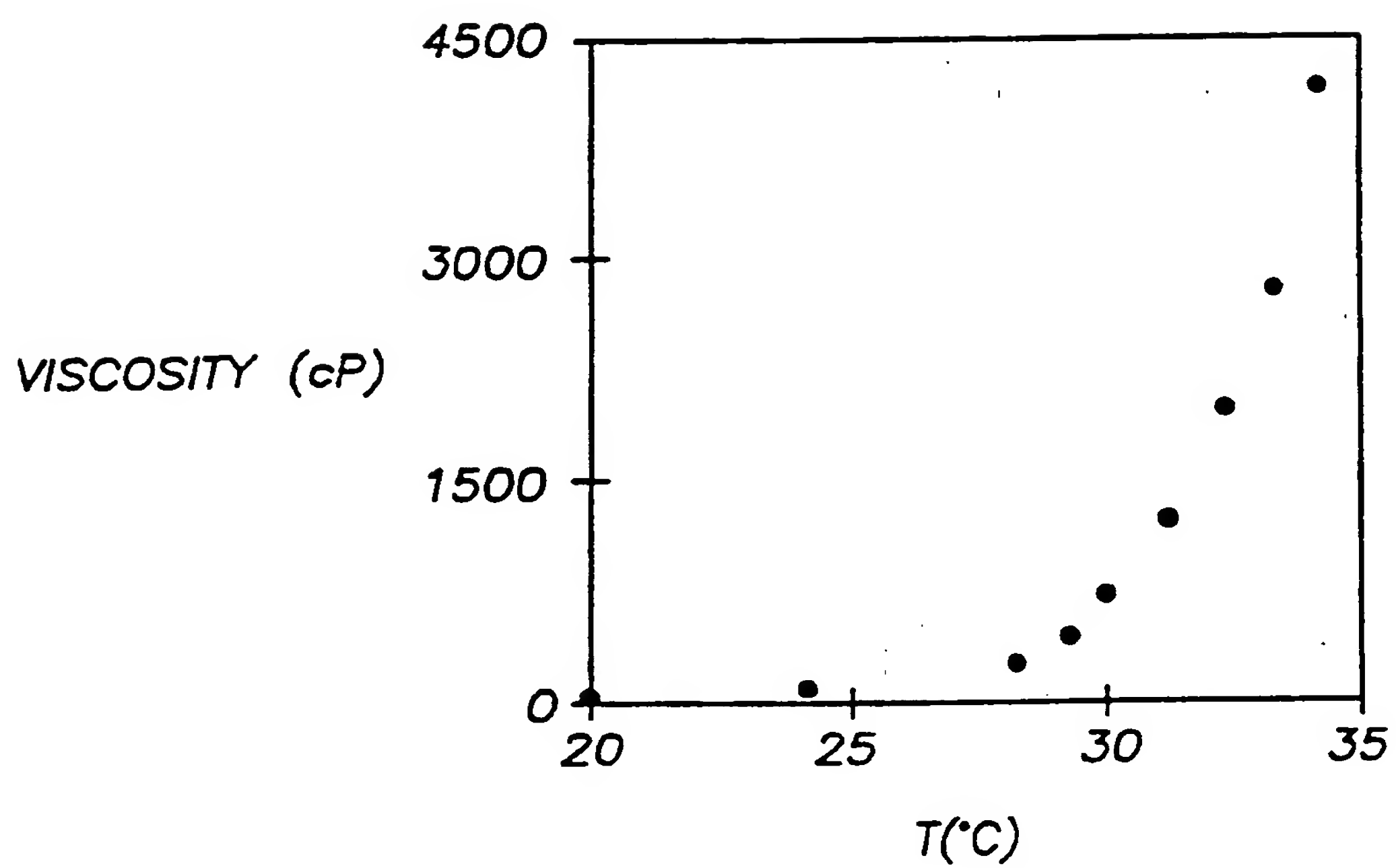
8/26

FIG. 8



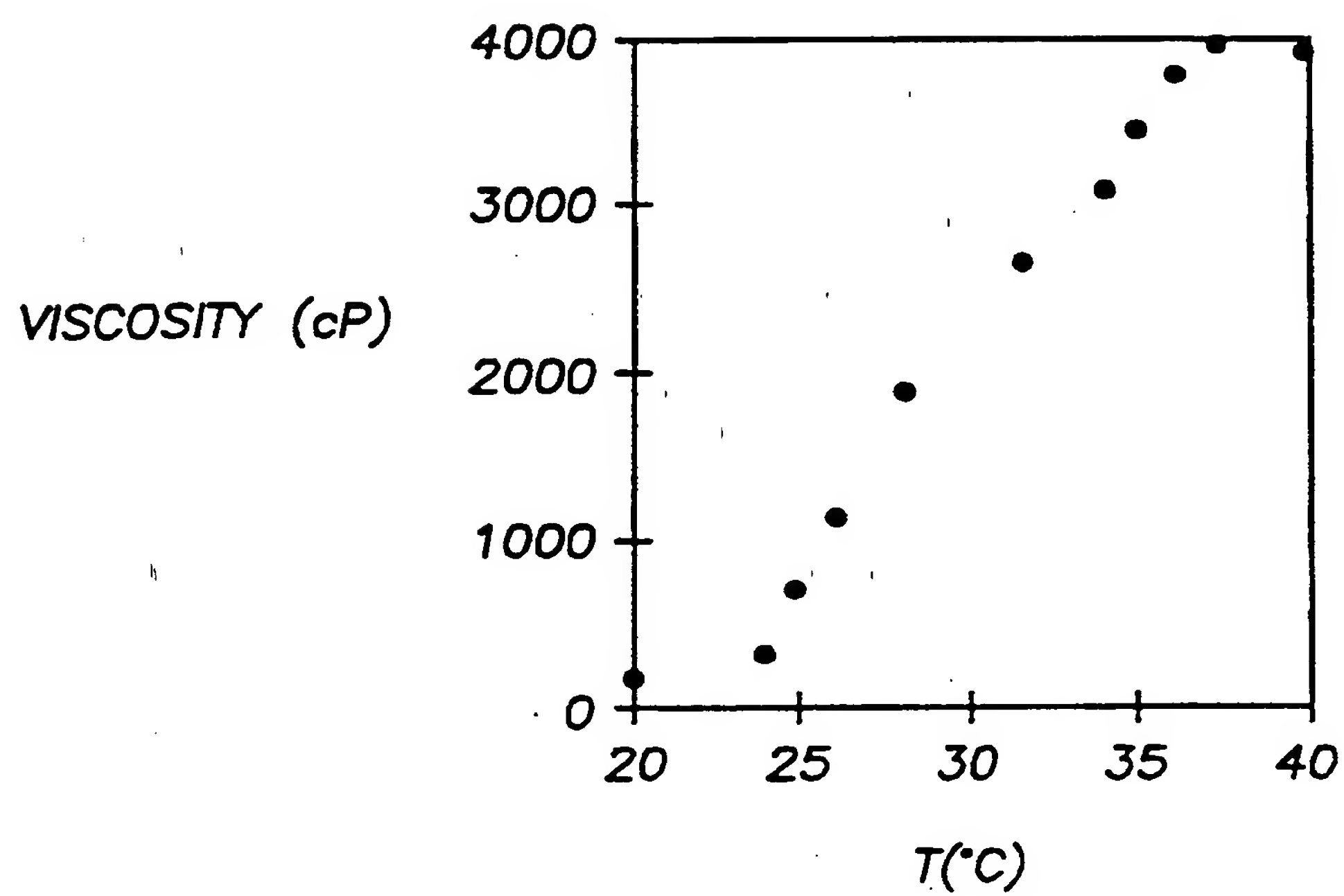
9/26

FIG. 9



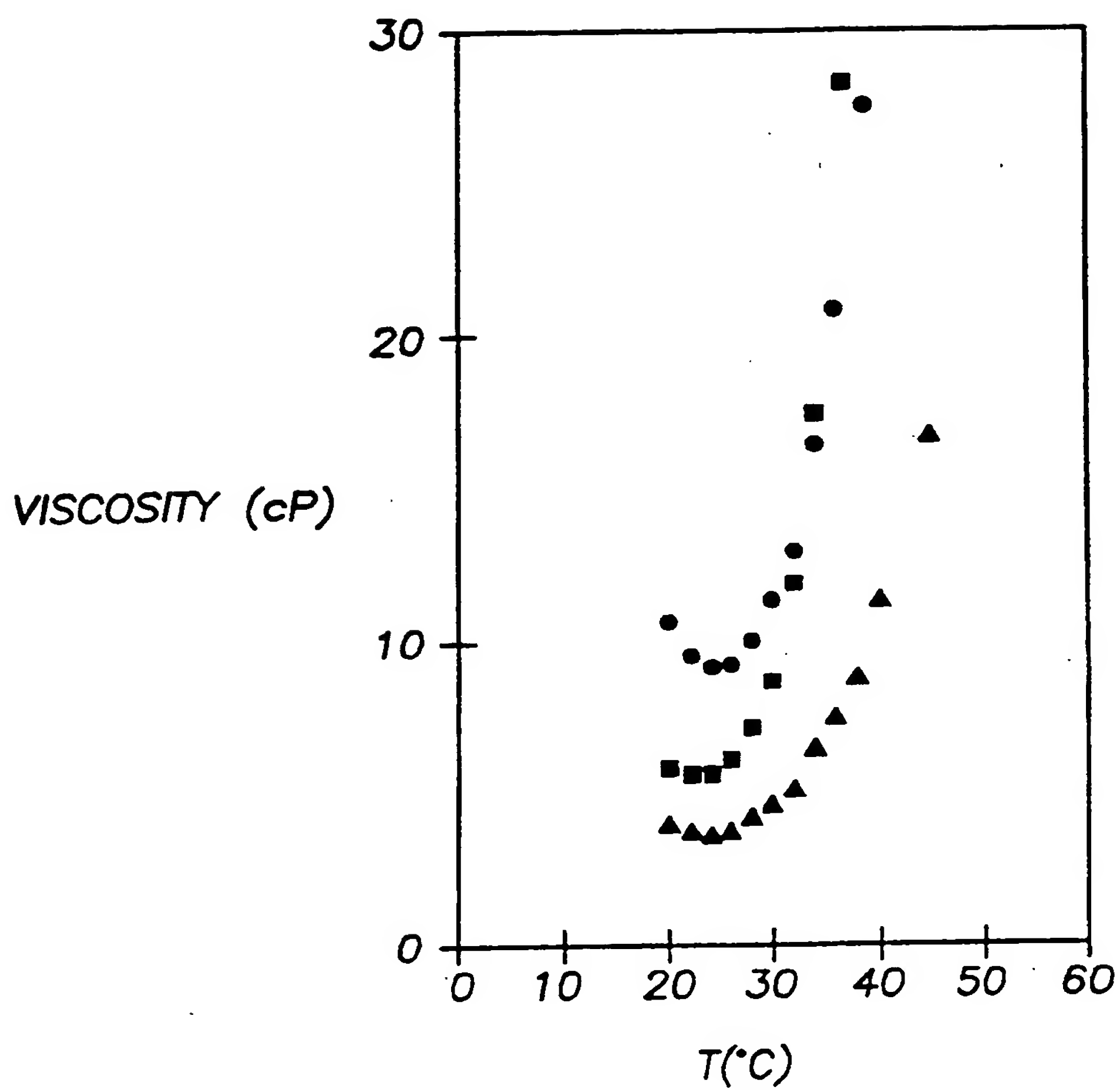
10/26

FIG. 10



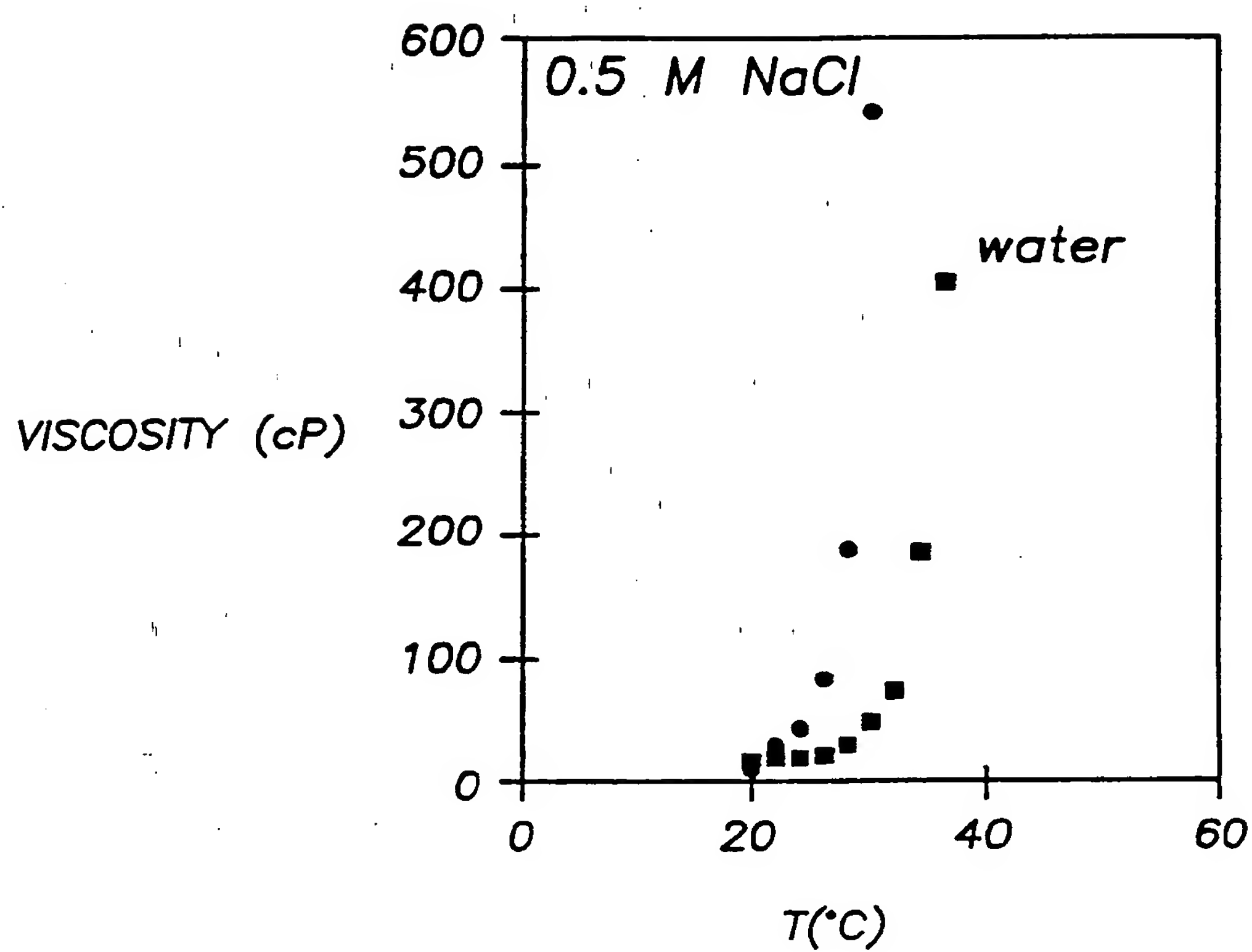
11/26

FIG. 11



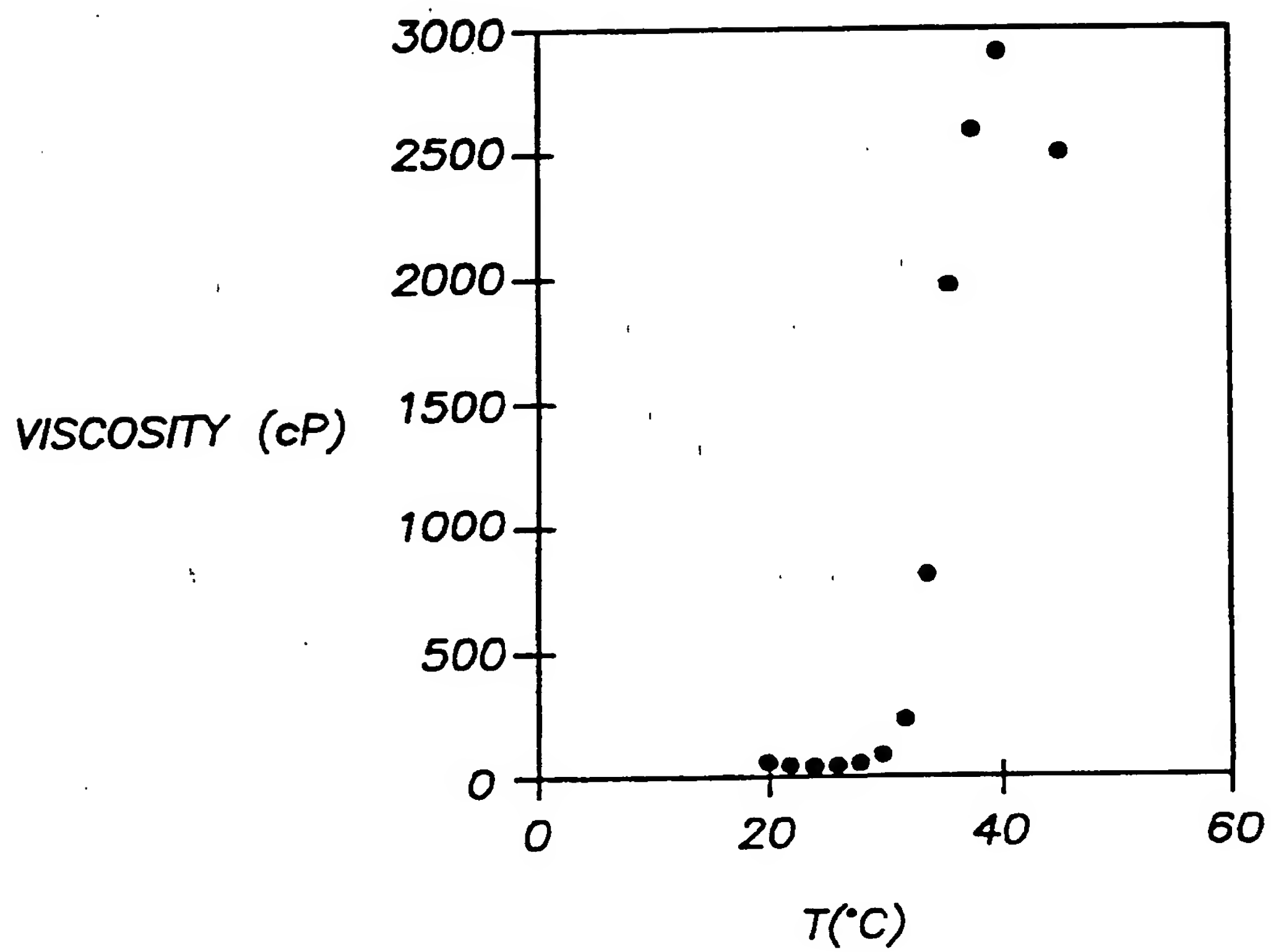
12/26

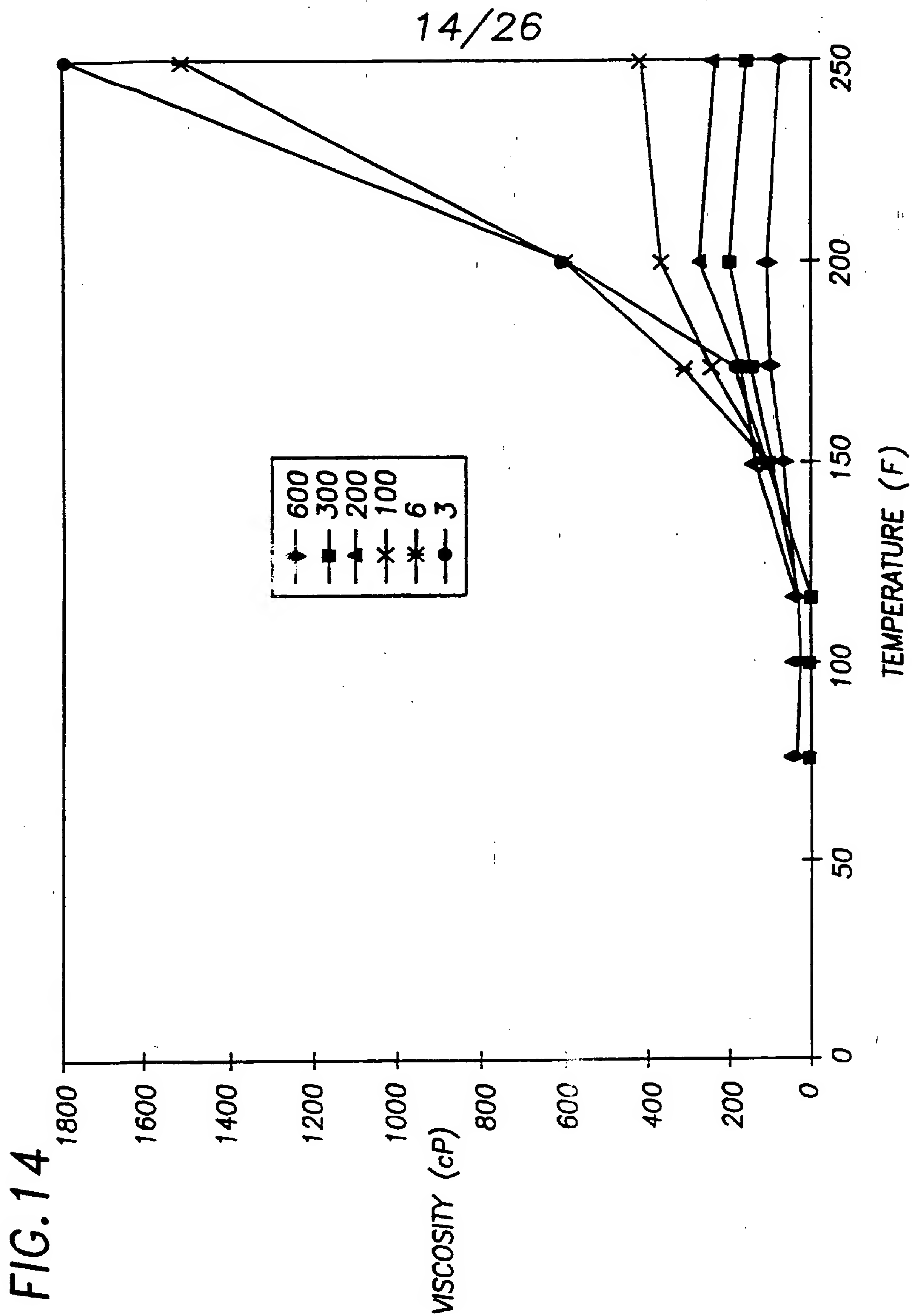
FIG. 12



13/26

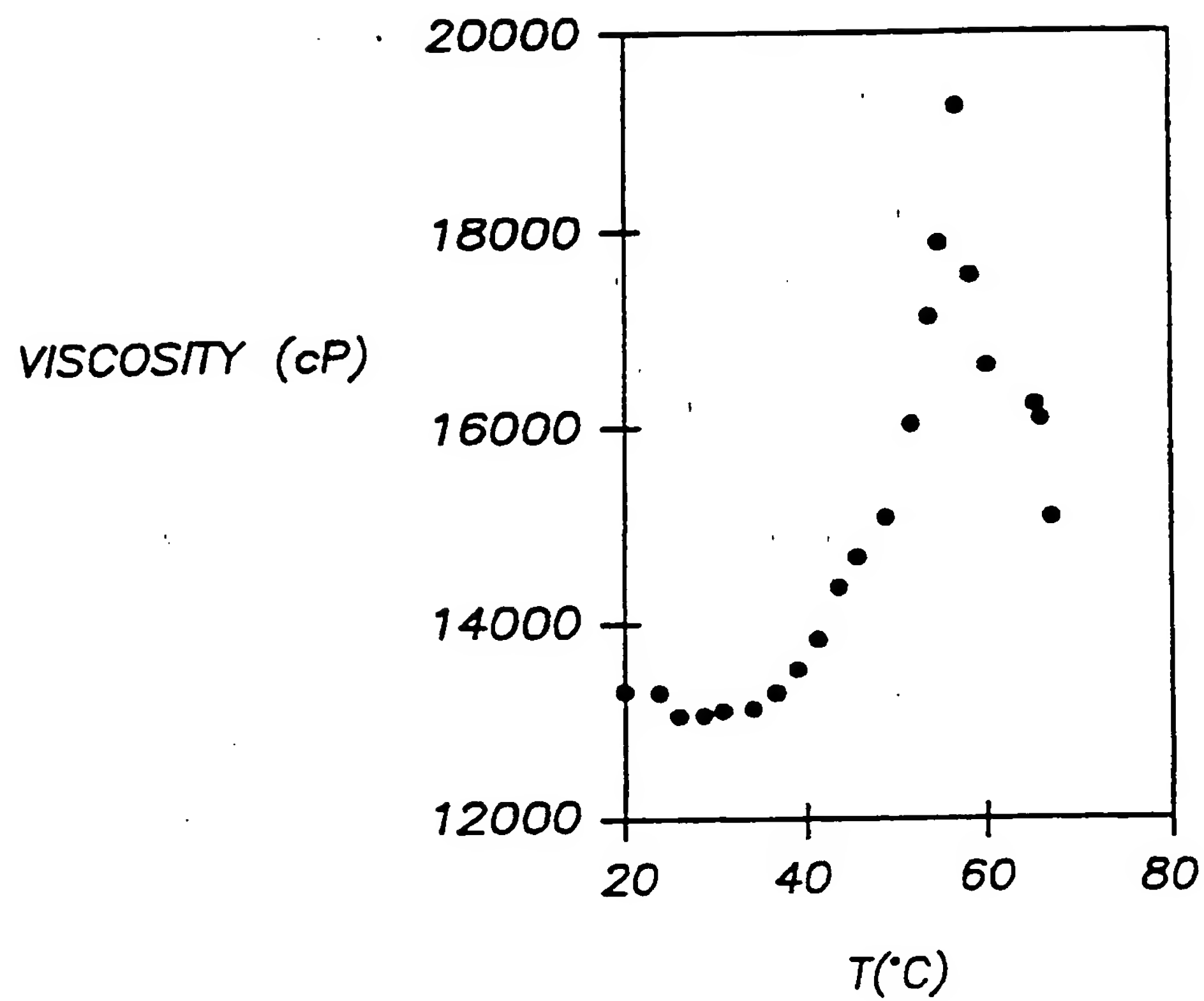
FIG. 13





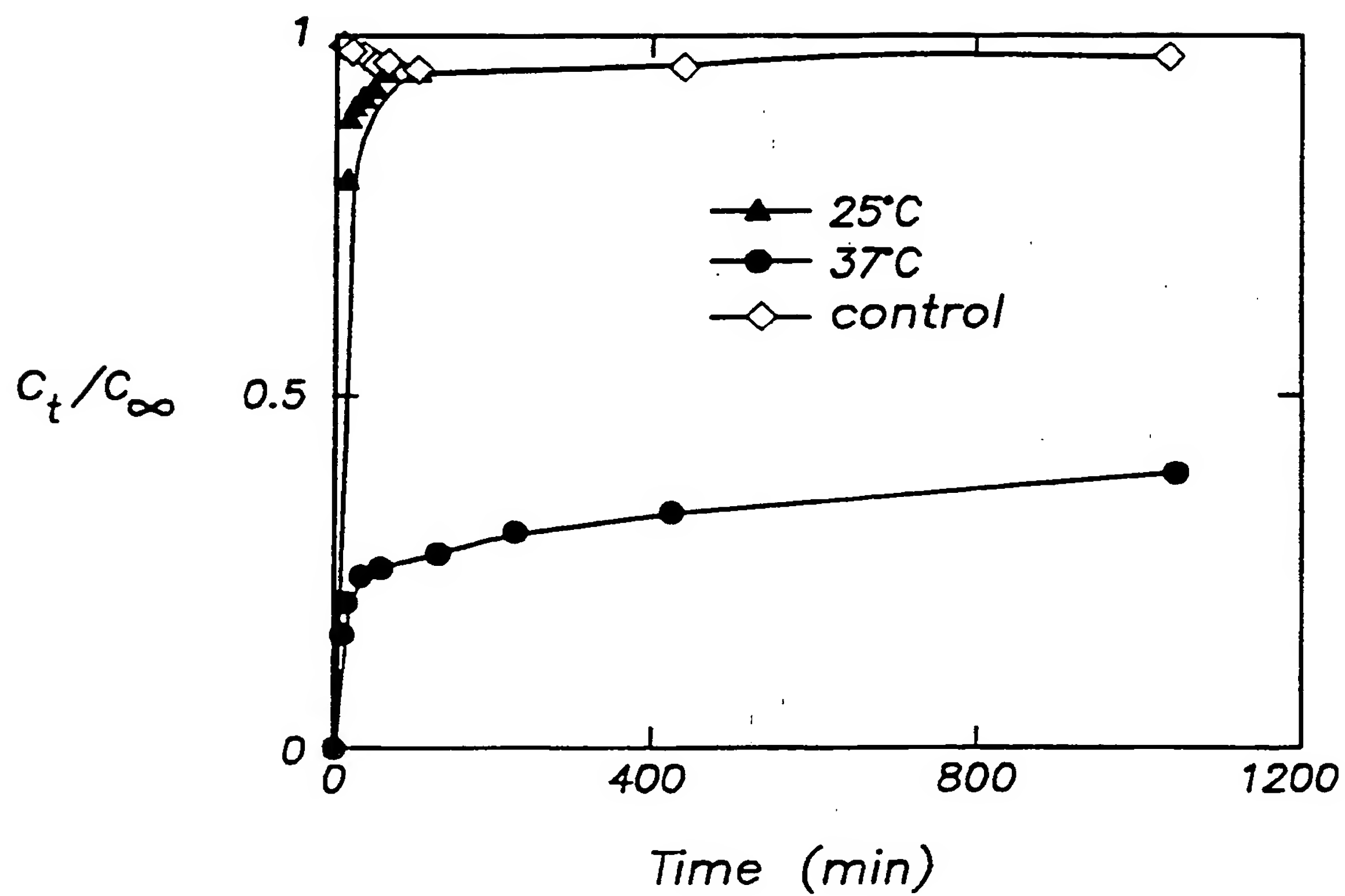
15/26

FIG. 15



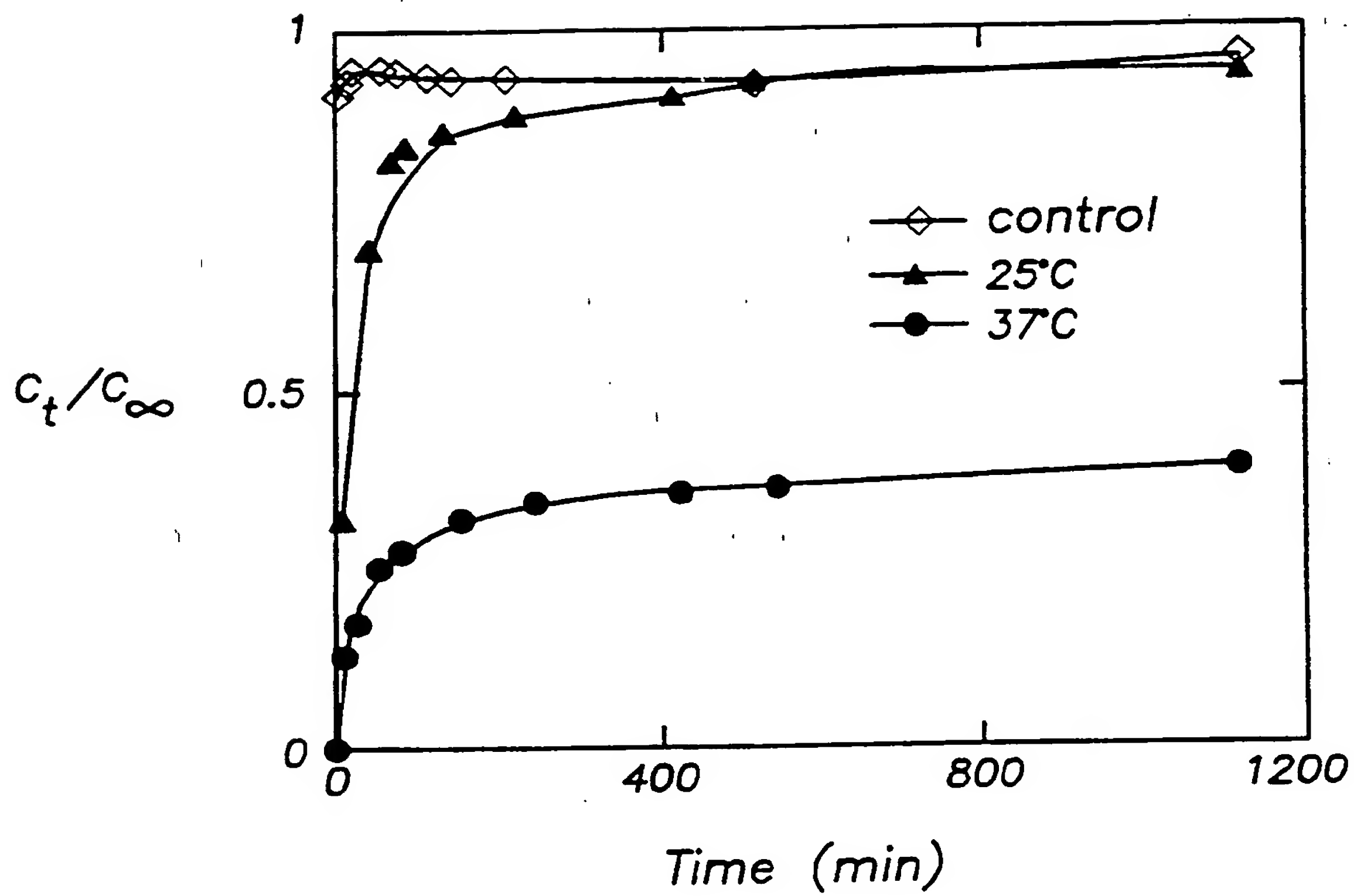
16/26

FIG. 16



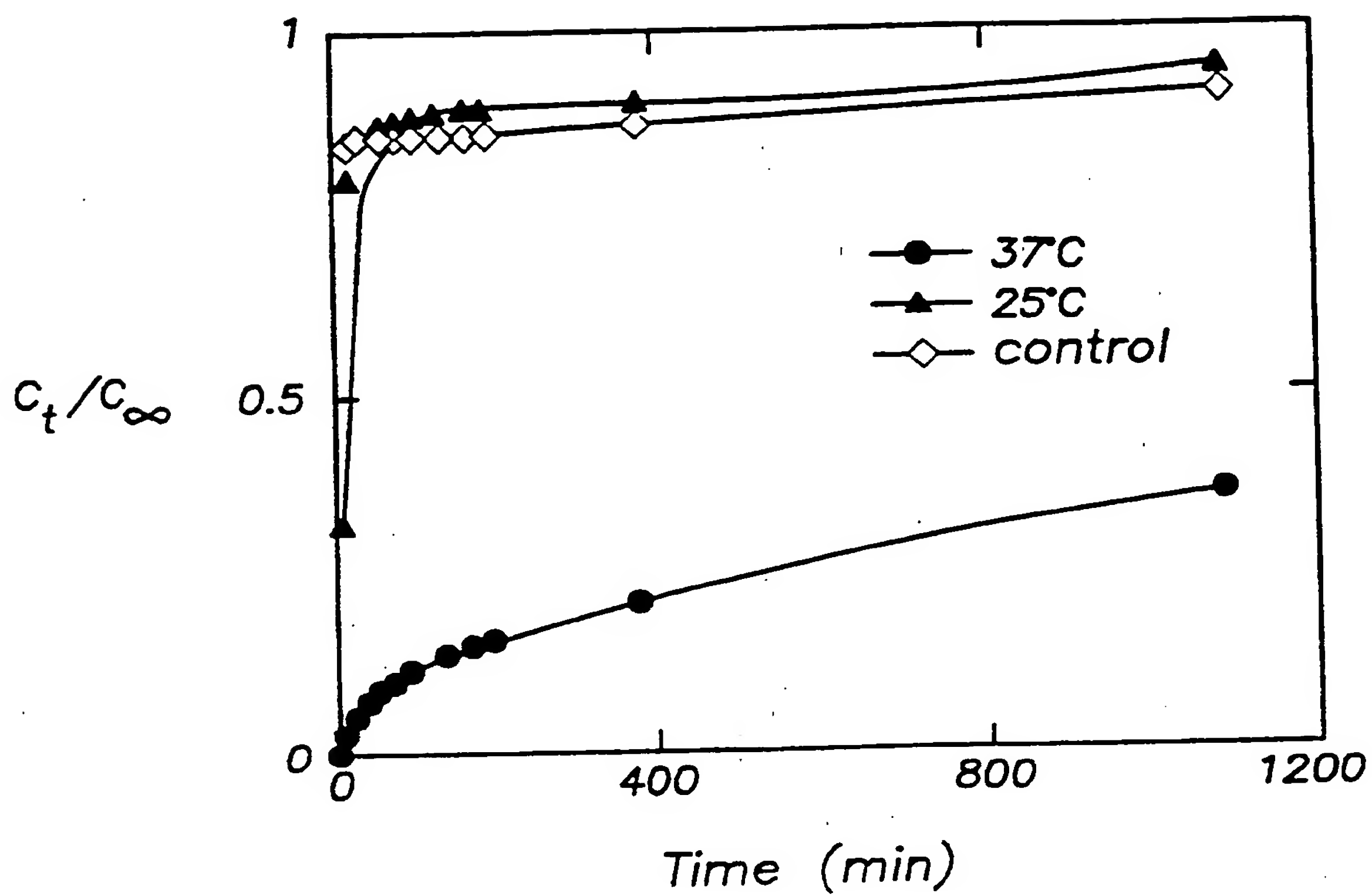
17/26

FIG. 17



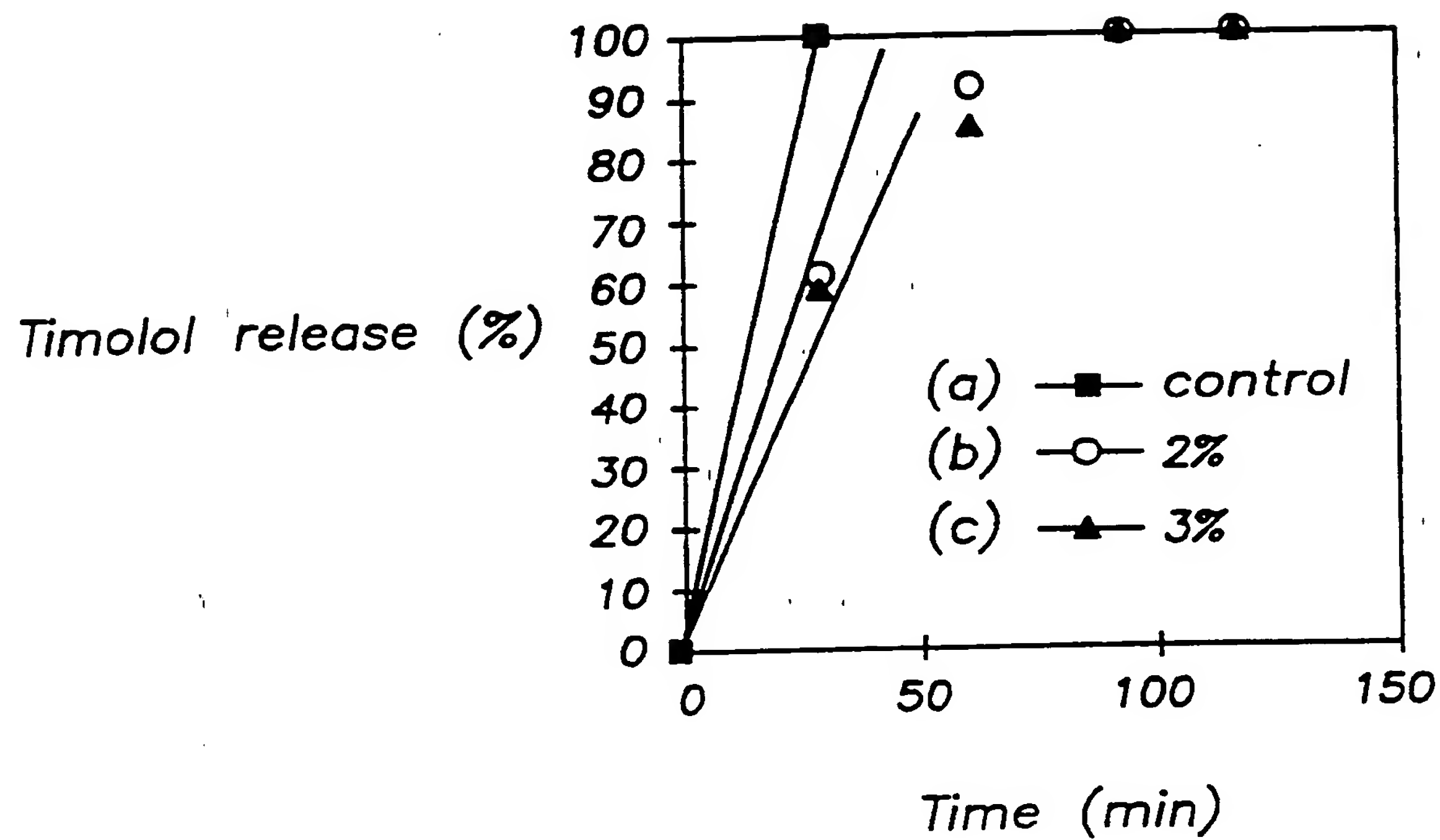
18/26

FIG. 18



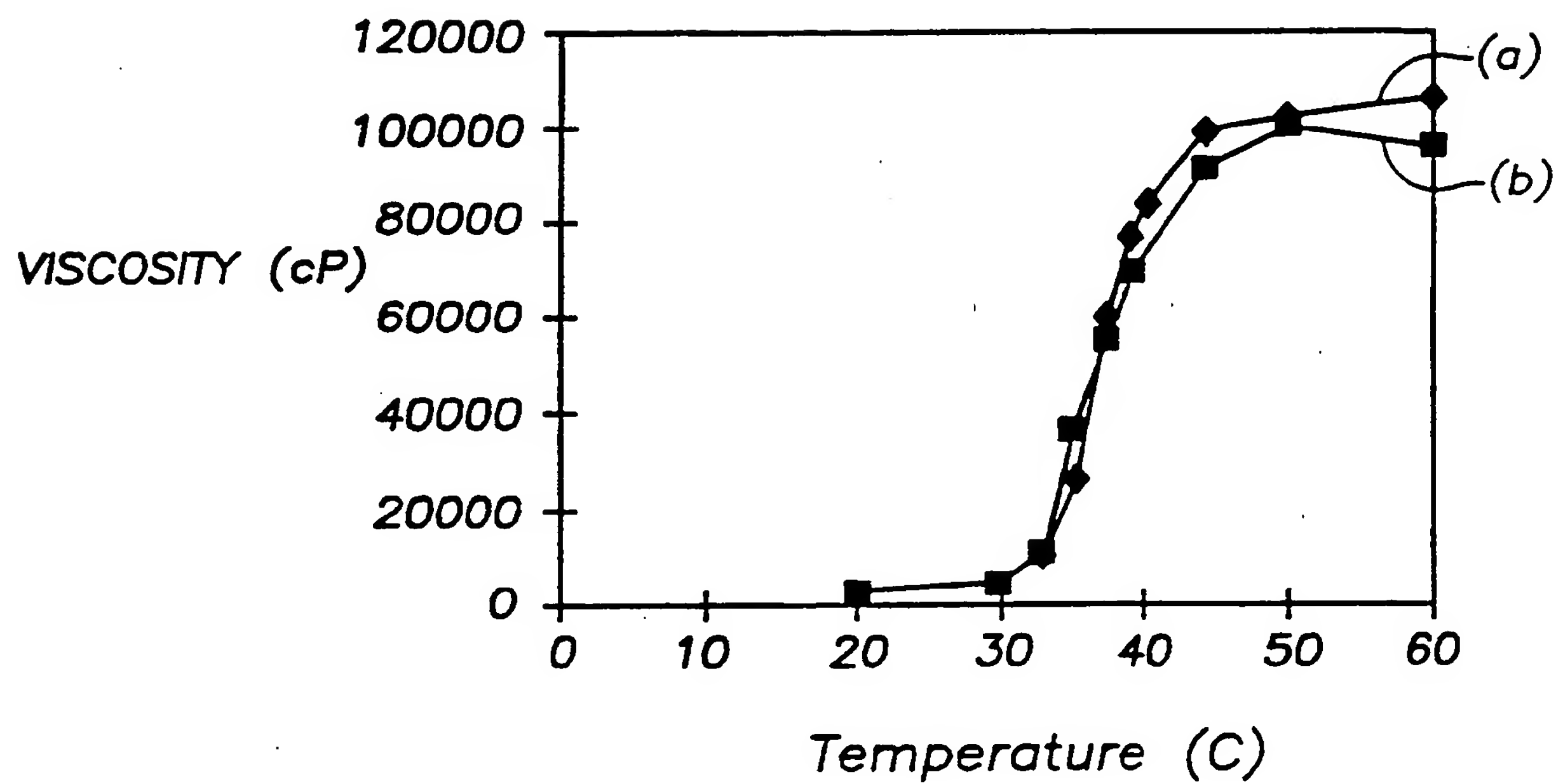
19/26

FIG. 19



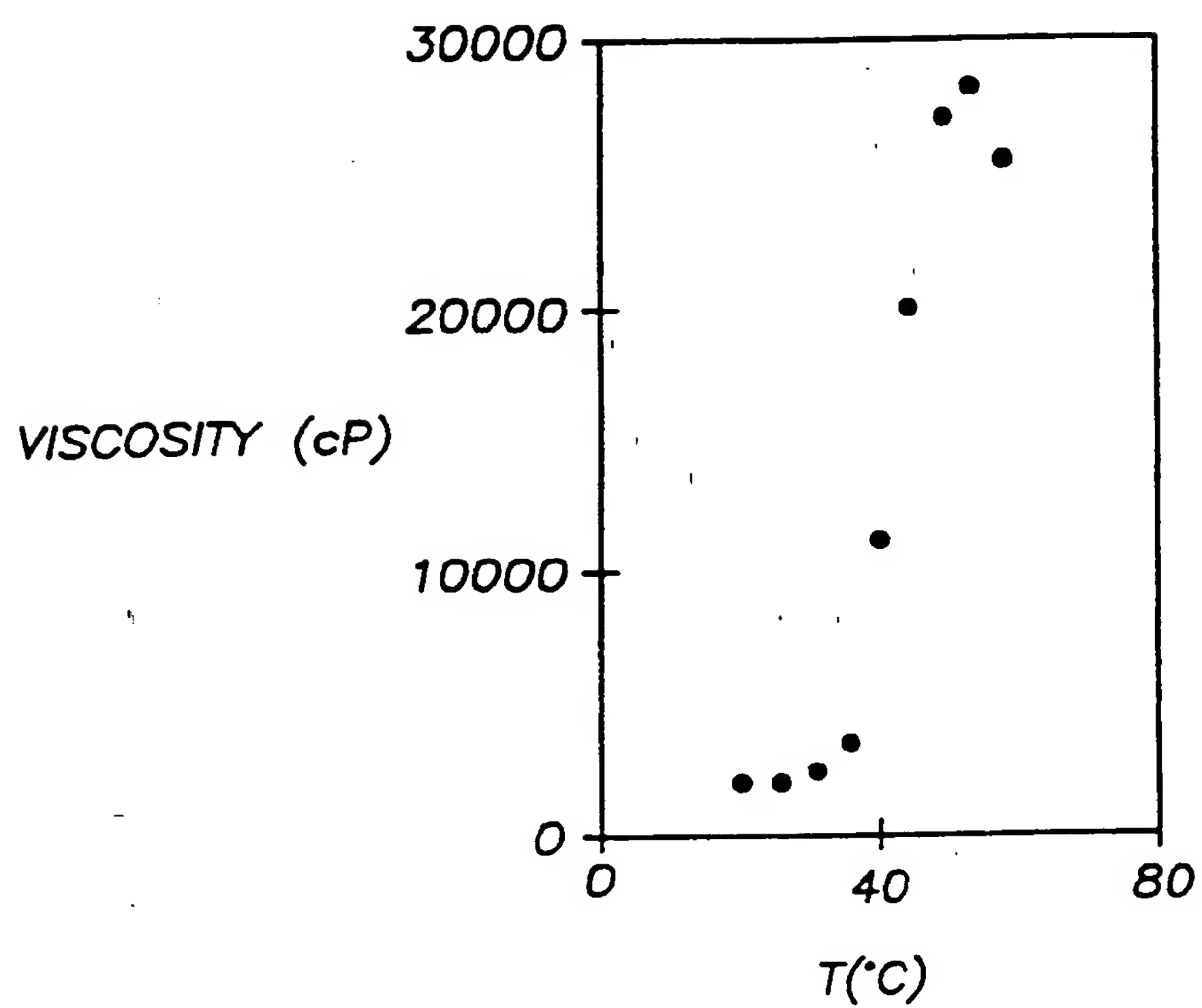
20/26

FIG. 20



21/26

FIG. 21



22/26

FIG. 22a

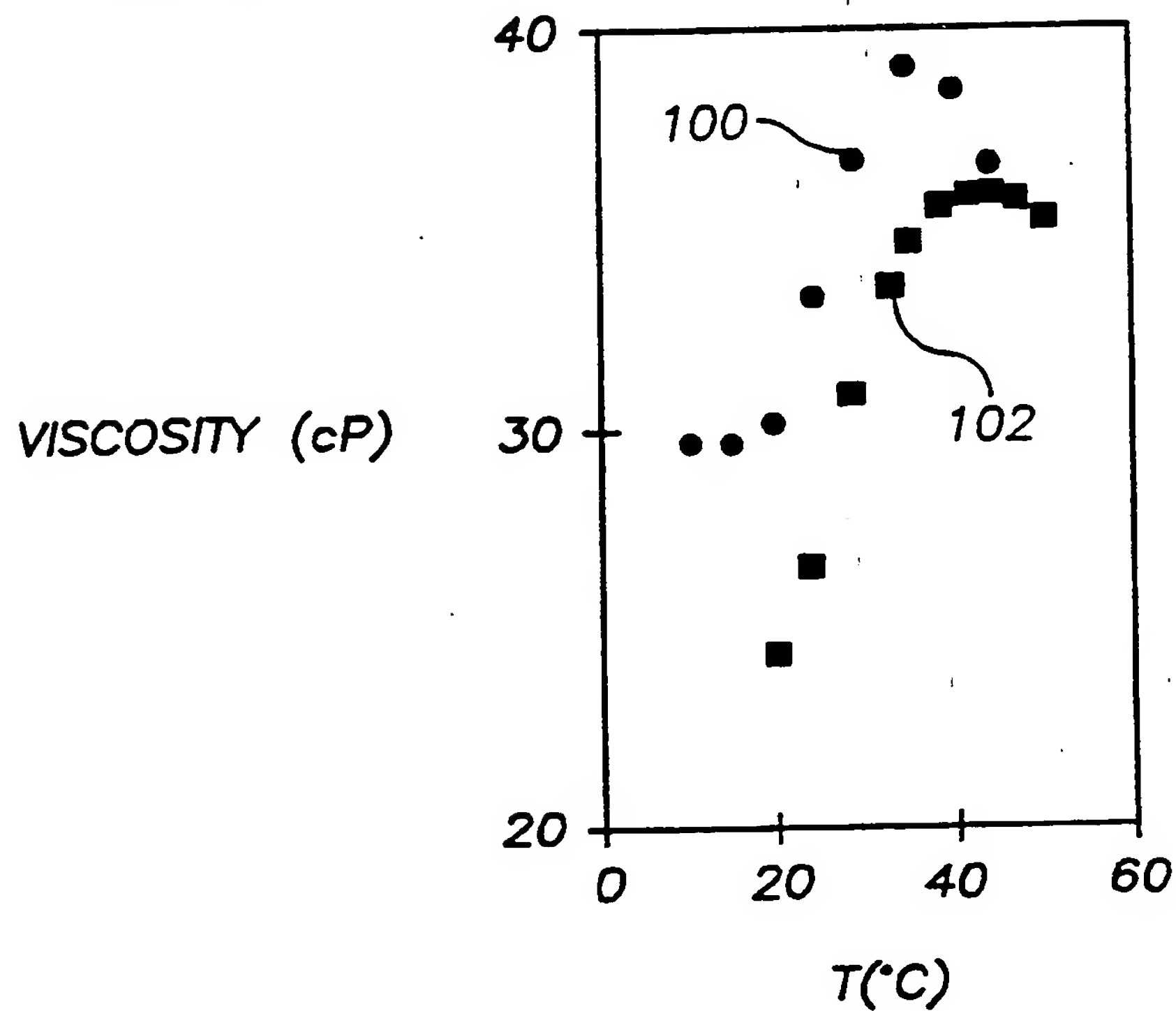
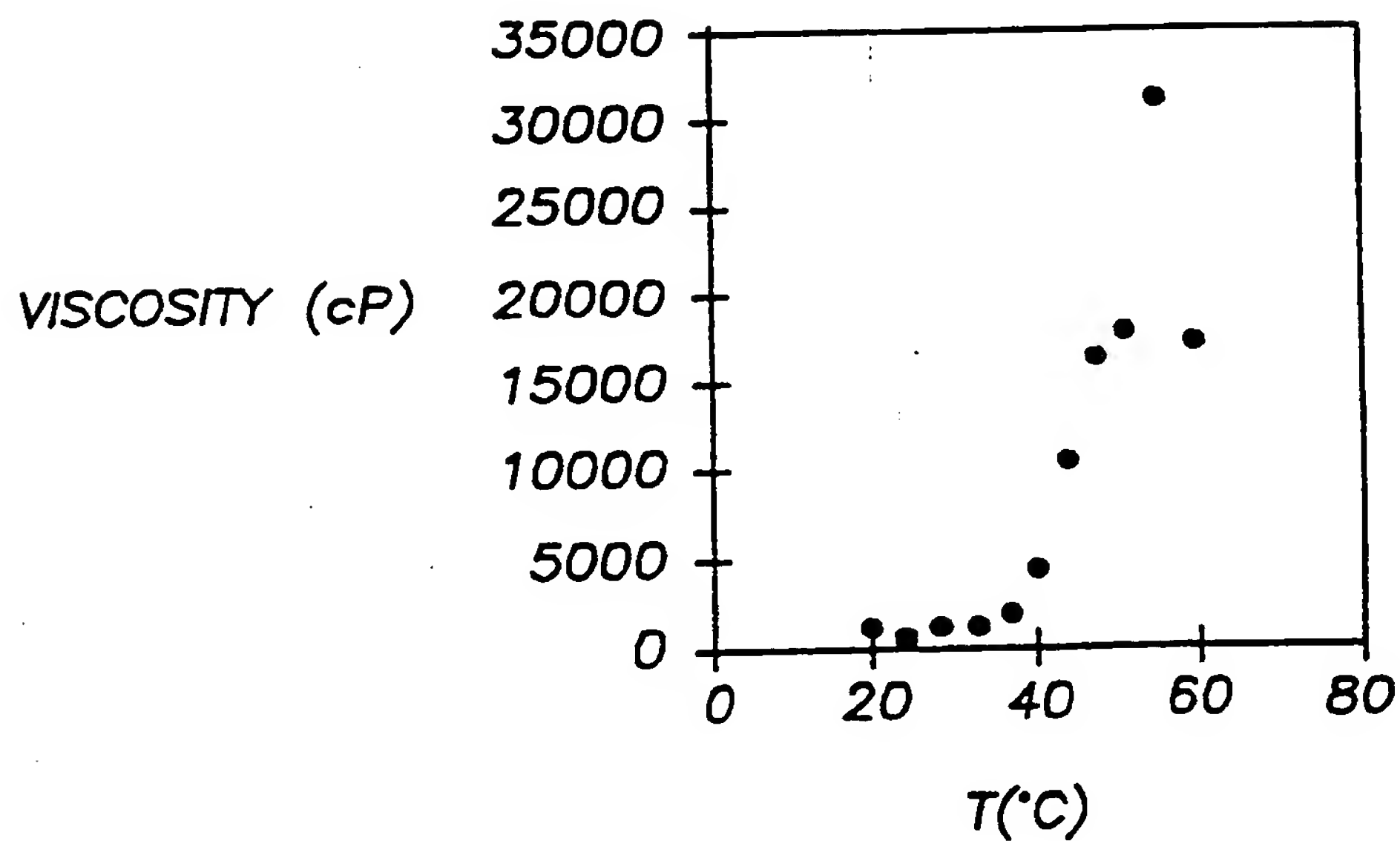
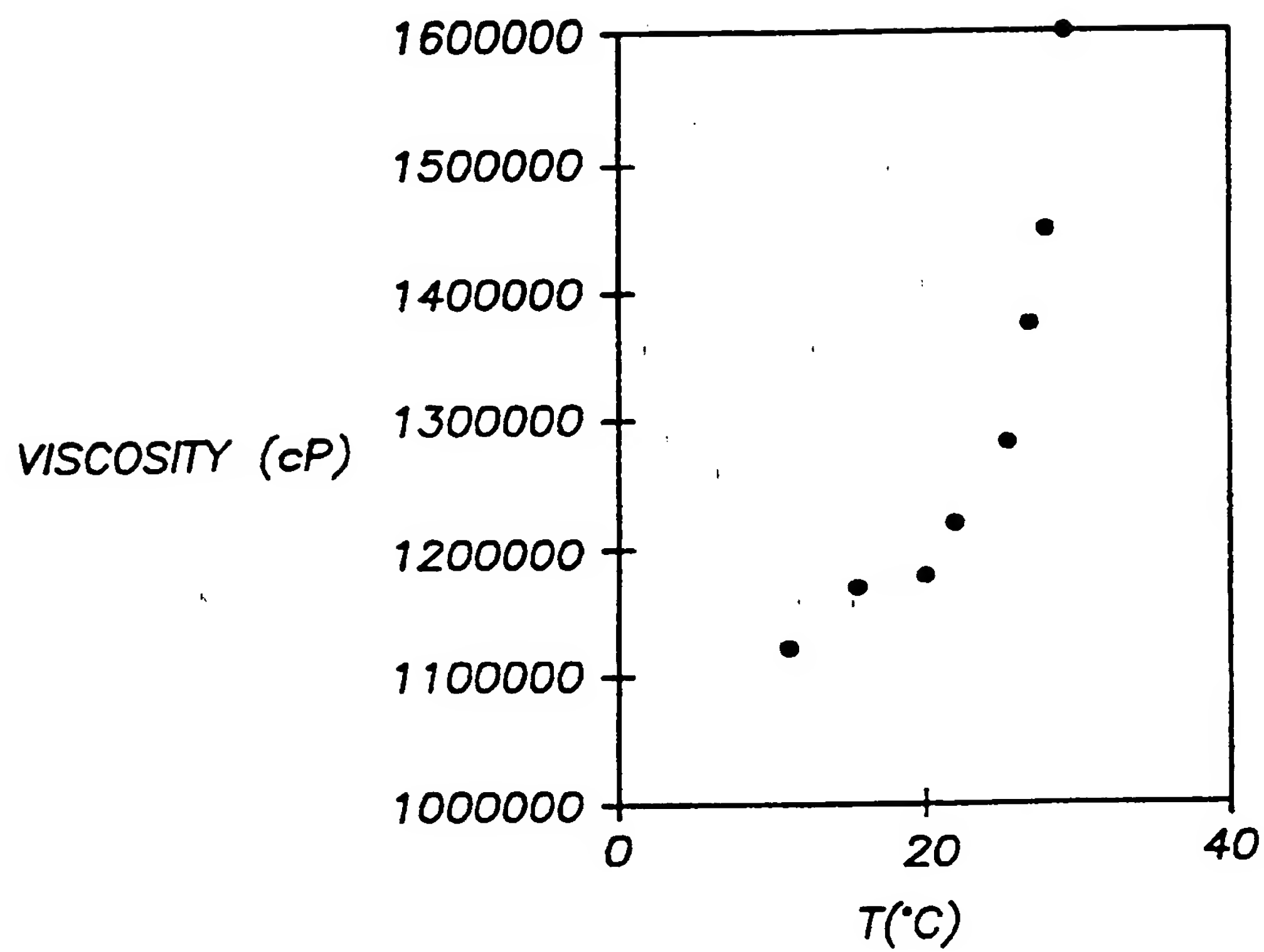


FIG. 22b



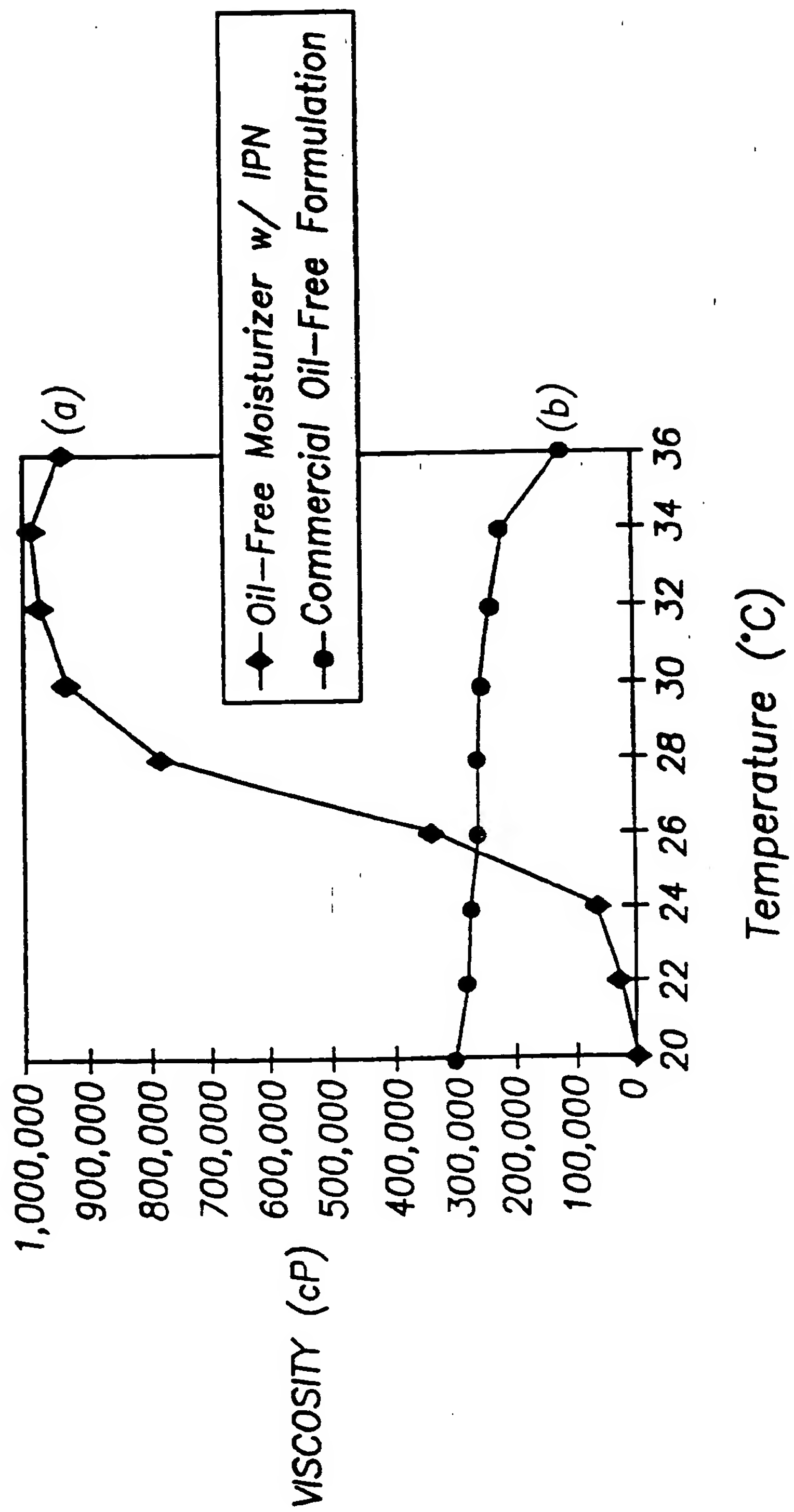
23/26

FIG. 23



24/26

FIG. 24



25/26

FIG. 25a

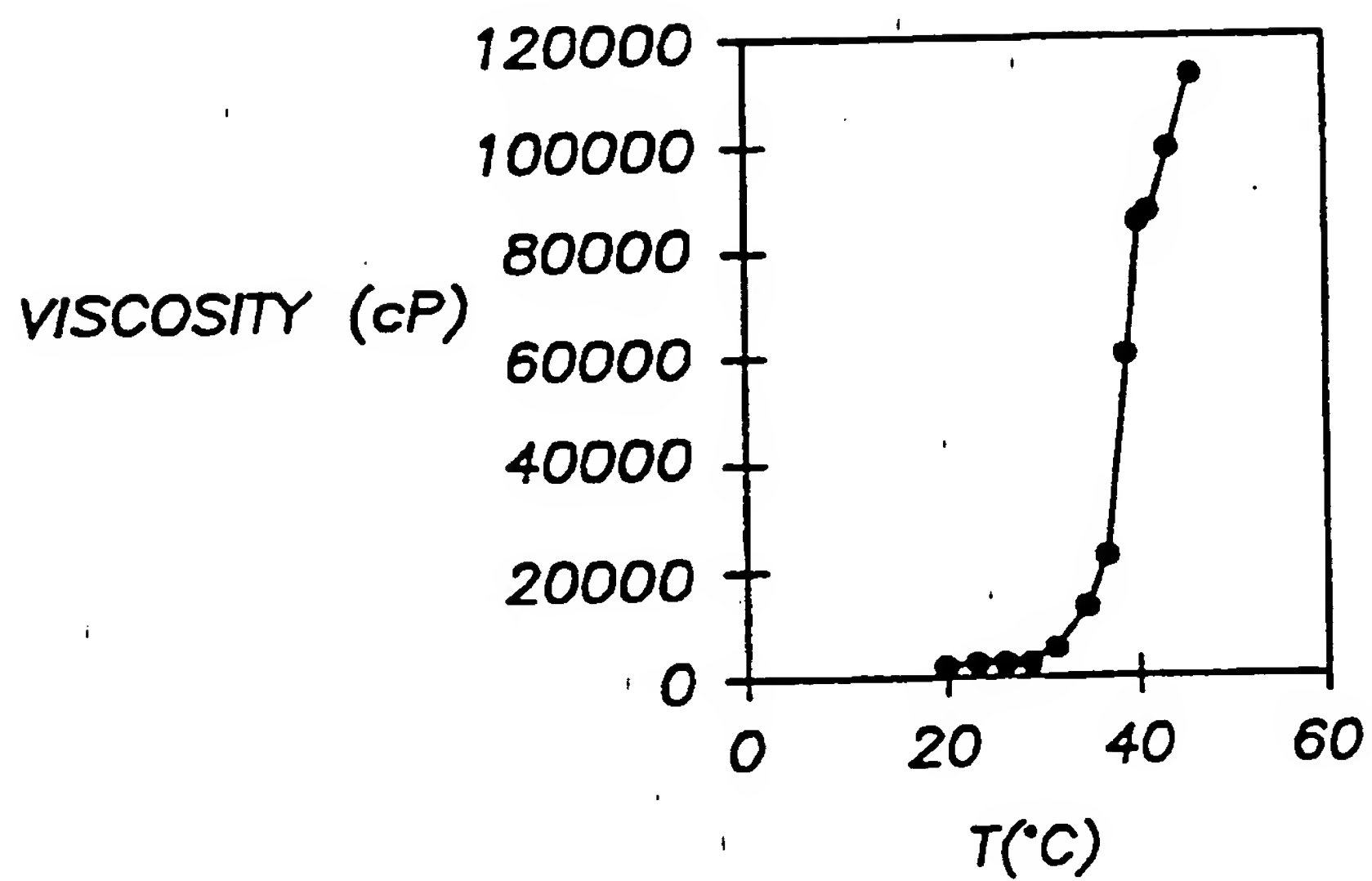
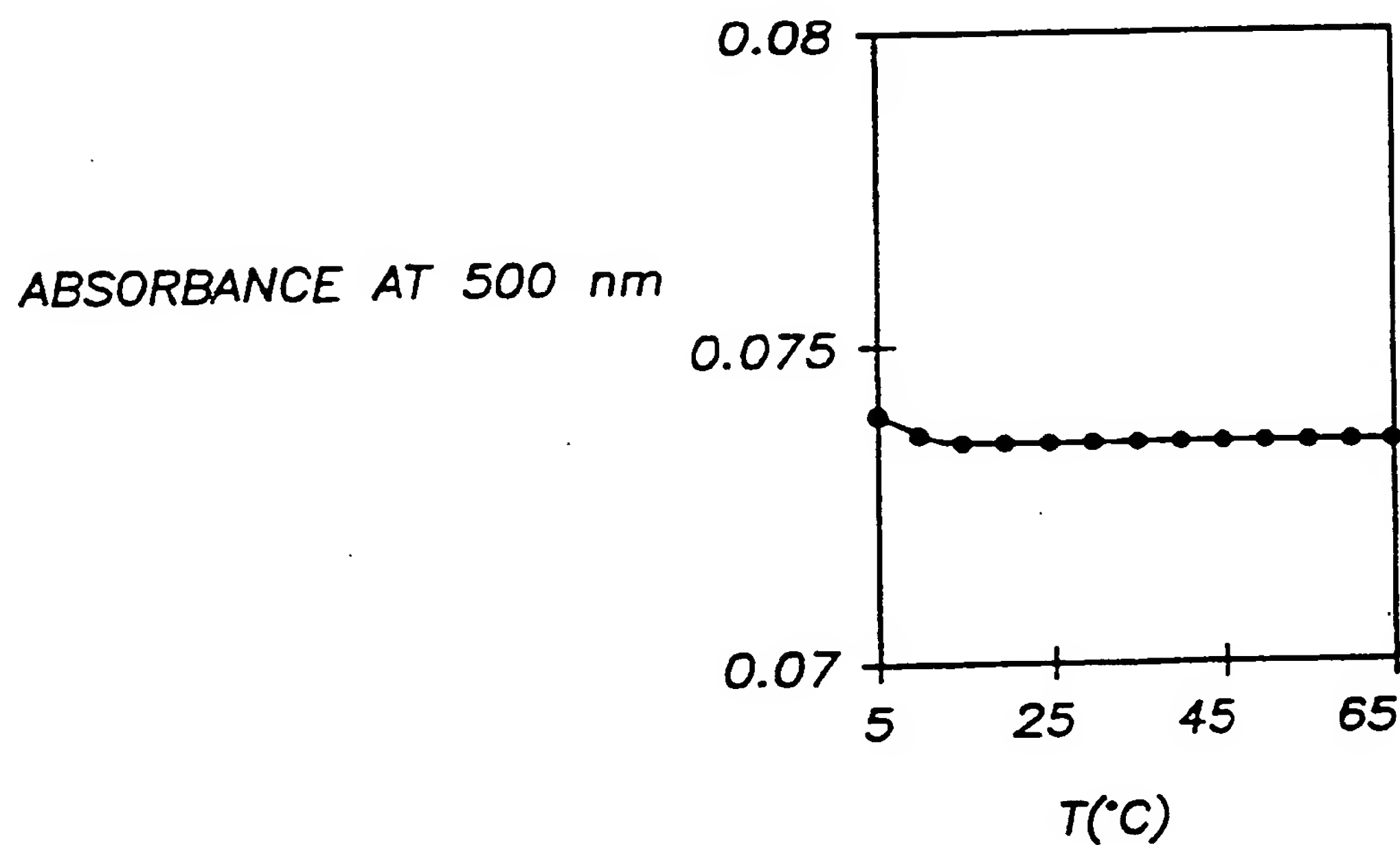


FIG. 25b



26/26

FIG. 26a

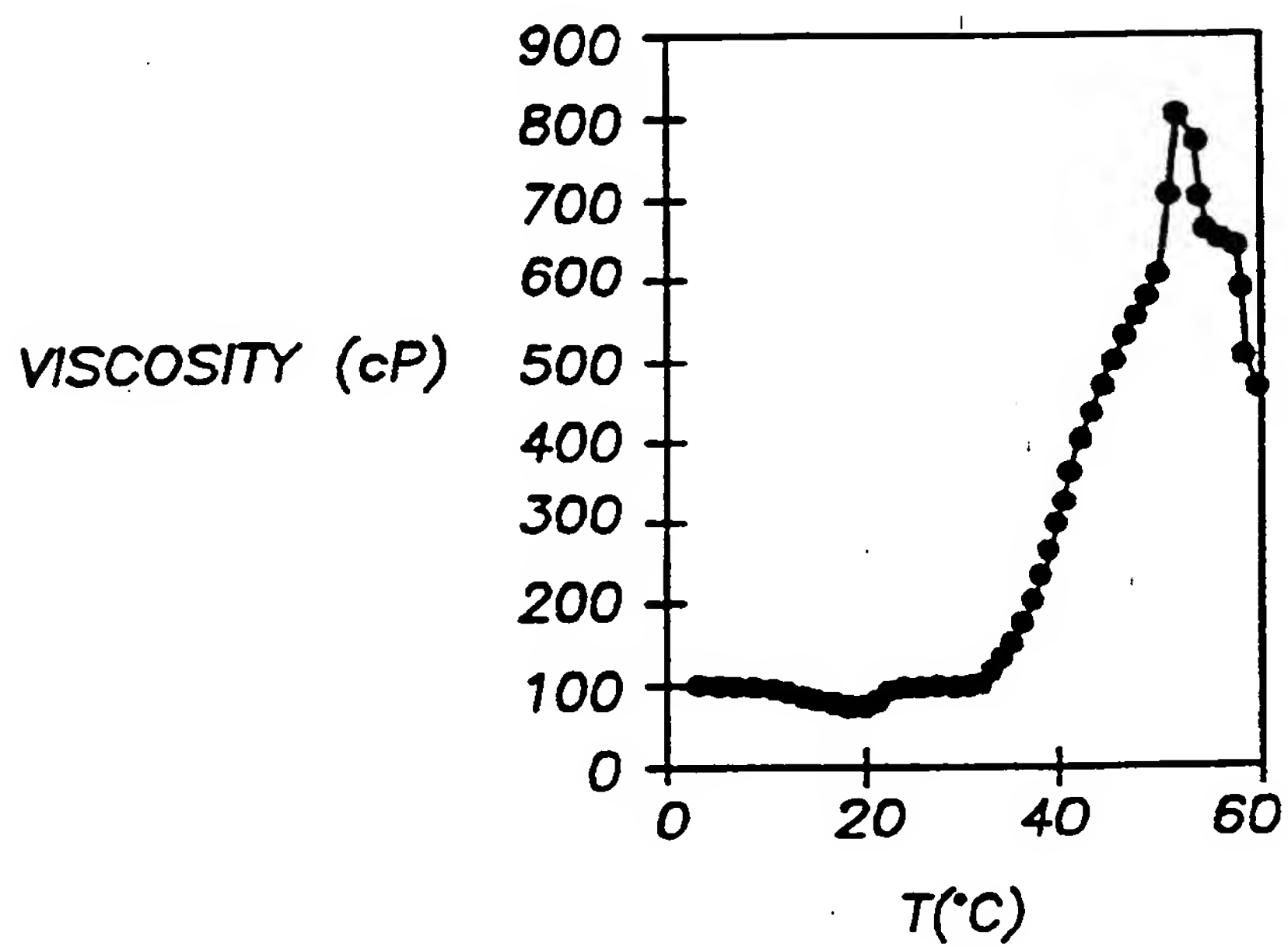
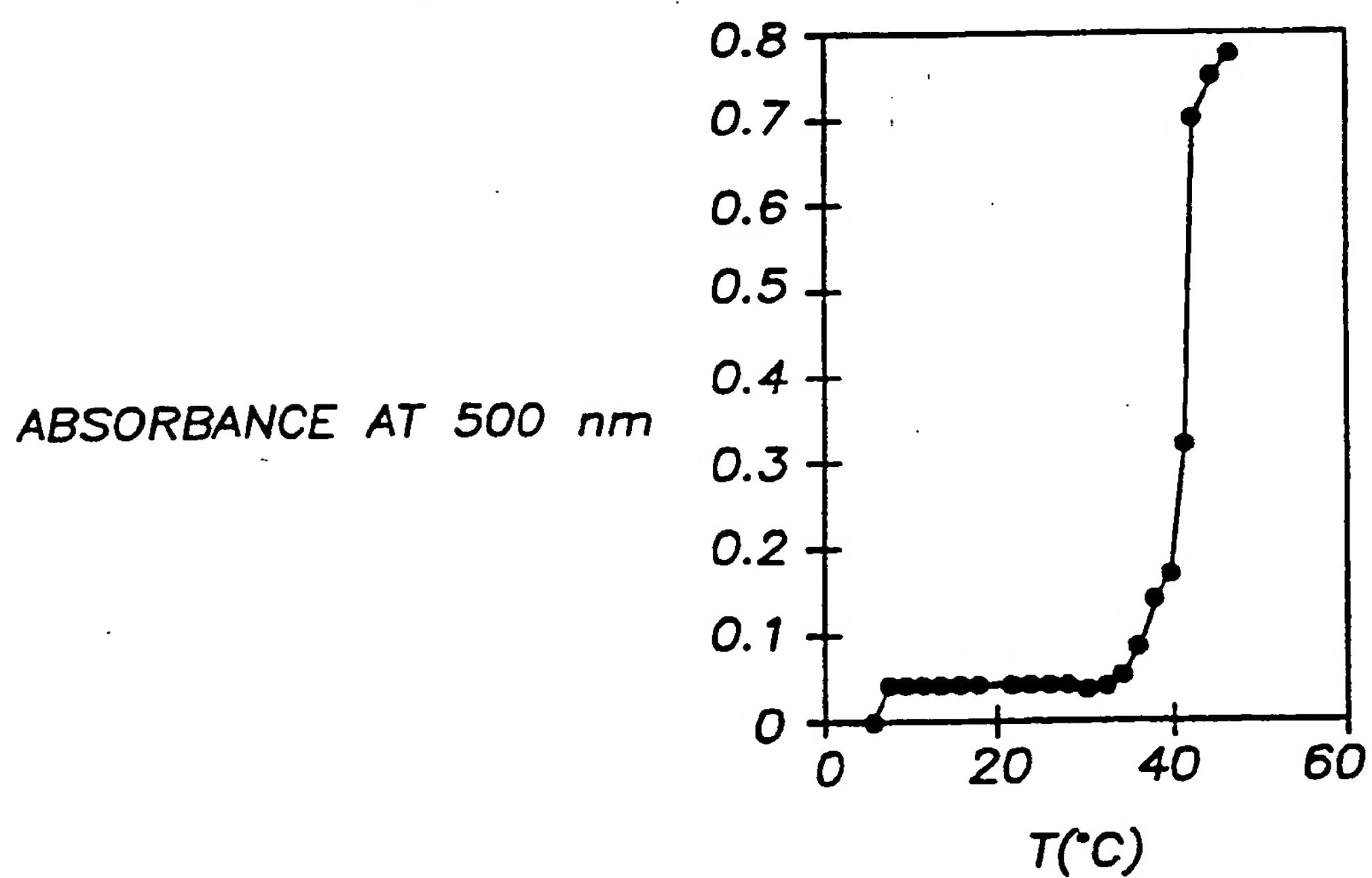


FIG. 26b



PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C08J 3/075		A3	(11) International Publication Number: WO 97/00275
			(43) International Publication Date: 3 January 1997 (03.01.97)
(21) International Application Number: PCT/US96/10376			01720 (US). MCKINNEY, George, W., III [-/US]; 33 Old Orchard Road, Chestnut Hill, MA 02167 (US). ORKISZ, Michal [-/US]; 12 Hatherly Road, Brighton, MA 02135 (US). HAND, Barry [-/US]; 7 Arlington Drive, Monroe, NY 01950 (US).
(22) International Filing Date: 14 June 1996 (14.06.96)			
(30) Priority Data:			
60/000,208 16 June 1995 (16.06.95) US			
60/000,312 19 June 1995 (19.06.95) US			
60/008,053 30 October 1995 (30.10.95) US			(74) Agent: SCOZZAFAVA, Mary, Rose; Choate, Hall & Stewart, Exchange Place, 53 State Street, Boston, MA 02109 (US).
08/580,986 3 January 1996 (03.01.96) US			
60/011,506 12 February 1996 (12.02.96) US			
60/012,221 21 February 1996 (21.02.96) US			
60/012,869 3 March 1996 (03.03.96) US			
60/012,868 5 March 1996 (05.03.96) US			(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).
60/017,158 20 May 1996 (20.05.96) US			
(71) Applicant (for all designated States except US): GEL SCIENCES, INC. [US/US]; 213 Burlington Road, Bedford, MA 01730 (US).			
(72) Inventors; and			
(75) Inventors/Applicants (for US only): BROMBERG, Lev [-/US]; 24 Mace Place #3, Lynn, MA 01902 (US). LUPTON, E., Cornelius [-/US]; 23 Pinckney Street, Boston, MA 02114 (US). SCHILLER, Matthew, E. [-/US]; 23C Sagamore Way, Waltham, MA 02154 (US). TIMM, Mary, J. [-/US]; Unit A1, 209 Great Road, Acton, MA			
			Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
			(88) Date of publication of the international search report: 6 March 1997 (06.03.97)
(54) Title: POLYMER NETWORKS RESPONSIVE TO CHANGES IN ENVIRONMENTAL STIMULI AND METHODS OF THEIR USE			
(57) Abstract			
A polymer network exhibiting the property of reversible gelation in response to a change in an environmental stimulus is provided. The solvated network polymer, comprises about 0.01 to 20 wt.% of an associating component linked to about 0.01 to 20 wt.% of a solvophilic component. The solvated composition exhibits at least a five-fold increase in viscosity upon gelation. The gelation may be triggered by a change in an environmental stimulus, such as temperature, pH and ionic strength.			

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Larvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
EE	Estonia	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	UG	Uganda
FI	Finland	MN	Mongolia	US	United States of America
FR	France	MR	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 96/10376

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C08J3/075

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C08J C08G C08F C08L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE WPI Section Ch, Week 9345 Derwent Publications Ltd., London, GB; Class A97, AN 93-357248 XP002022768 & JP,A,05 262 882 (GRACE & CO-CONN W R) , 12 October 1993 see abstract</p> <p style="text-align: center;">---</p>	1,3,5,10
X	<p>DATABASE WPI Section Ch, Week 9437 Derwent Publications Ltd., London, GB; Class A14, AN 94-299881 XP002022769 & JP,A,06 228 319 (TSUCHIDA H) , 16 August 1994 see abstract</p> <p style="text-align: center;">---</p> <p style="text-align: center;">-/-</p>	1,3

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- *&* document member of the same patent family

Date of the actual completion of the international search

15 January 1997

Date of mailing of the international search report

24. 01. 97

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+ 31-70) 340-3016

Authorized officer

Niaounakis, M

INTERNATIONAL SEARCH REPORT

International Application No
PCI/US 96/10376

C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US,A,5 252 318 (JOSHI ABHAY ET AL) 12 October 1993 cited in the application see claims 1,3 ---	1
A	DATABASE WPI Section Ch, Week 9515 Derwent Publications Ltd., London, GB; Class A23, AN 95-110686 XP002022770 & JP,A,07 033 844 (SAGAMI CHEM RES CENTRE) , 3 February 1995 see abstract ---	1
A	DATABASE WPI Section Ch, Week 9407 Derwent Publications Ltd., London, GB; Class A14, AN 94-054029 XP002022771 & JP,A,06 009 848 (SANYO CHEM IND LTD) , 18 January 1994 see abstract ---	1
A	WO,A,95 04774 (LVMH RECH ;ILIPOULOS ILIAS (FR); CARTALAS SARRAZIN ANNE (FR); LOY) 16 February 1995 see claim 1 ---	1
P,A	WO,A,95 24430 (UNIV WASHINGTON ;ALCON LAB INC (US)) 14 September 1995 cited in the application see claims 1,35-41 ---	1
E	WO,A,96 28056 (GEL SCIENCES INC ;MCKINNEY GEORGE W (US); TANENBAUM JAMES (US); LE) 19 September 1996 see page 1, line 17 - page 4, line 5 see examples -----	1-28,30, 34-52, 67,71

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 96/10376

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A-5252318	12-10-93	AT-T- 134508	15-03-96
		AU-A- 8201391	07-01-92
		DE-D- 69117509	04-04-96
		DE-T- 69117509	19-09-96
		EP-A- 0533836	31-03-93
		ES-T- 2083581	16-04-96
		IL-A- 98320	31-10-95
		WO-A- 9119481	26-12-91
		US-A- 5441732	15-08-95

WO-A-9504774	16-02-95	FR-A- 2708616	10-02-95
		EP-A- 0712422	22-05-96

WO-A-9524430	14-09-95	AU-A- 2093295	25-09-95
		CA-A- 2184814	14-09-95
		EP-A- 0748342	18-12-96

WO-A-9628056	19-09-96	AU-A- 5252996	02-10-96
		AU-A- 5523996	02-10-96
		AU-A- 5850196	02-10-96
		WO-A- 9628057	19-09-96
		WO-A- 9628055	19-09-96
		WO-A- 9700275	03-01-97
